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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 417/06, 413/06, 417/14, A61K 31/425, 31/42 — A1

(11) International Publication Number: **WO 96/26207**

(43) International Publication Date: 29 August 1996 (29.08.96)

(21) International Application Number: PCT/JP96/00403

(22) International Filing Date: 22 February 1996 (22.02.96)

(30) Priority Data:
7/34963 23 February 1995 (23.02.95) JP
7/336391 25 December 1995 (25.12.95) JP

(71) Applicant *(for all designated States except US)*: NISSAN CHEMICAL INDUSTRIES, LTD. [JP/JP]; 7-1, Kanda-Nishiki-cho 3-chome, Chiyoda-ku, Tokyo 101 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: OHARA, Yoshio [JP/JP]; Nissan Chemical Industries, Ltd., Central Research Institute, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 274 (JP). SUZUKI, Mikio [JP/JP]; Nissan Chemical Industries, Ltd., Central Research Institute, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 274 (JP). OHDOI, Keisuke [JP/JP]; Nissan Chemical Industries, Ltd., Central Research Institute, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 274 (JP). MIYACHI, Nobuhide [JP/JP]; Nissan Chemical Industries, Ltd., Central Research Institute, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 274 (JP). KATO, Katsuhiro [JP/JP]; Nissan Chemical Industries, Ltd., Central Research Institute, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 274 (JP). KOBAYASHI, Tetsuya [JP/JP]; Nissan Chemical Industries, Ltd., Central Research Institute, 722-1, Tsuboi-cho, Funabashi-shi, Chiba 274 (JP). SHIKADA, Ken-ichi [JP/JP]; Nissan Chemical Industries, Ltd., Seibutsukagaku Kenkyusho, 1470, Oaza-shiraoka, Shiraoka-machi, Minamisaitama-gun, Saitama 349-02 (JP). KITAHARA, Masaki [JP/JP]; Nissan Chemical Industries, Ltd., Seibutsukagaku Kenkyusho, 1470, Oaza-shiraoka, Shiraoka-machi, Minamisaitama-gun, Saitama 349-02 (JP). NAITO, Takeshi [JP/JP]; Nissan Chemical Industries, Ltd., Seibutsukagaku Kenkyusho, 1470, Oaza-shiraoka, Shiraoka-machi, Minamisaitama-gun, Saitama 349-02 (JP). YOTSUMOTO, Takashi [JP/JP]; Nissan Chemical Industries, Ltd., Seibutsukagaku Kenkyusho, 1470, Oaza-shiraoka, Shiraoka-machi, Minamisaitama-gun, Saitama 349-02 (JP). MIYAKOSHI, Chie [JP/JP]; Nissan Chemical Industries, Ltd., Seibutsukagaku Kenkyusho, 1470, Oaza-shiraoka, Shiraoka-machi, Minamisaitama-gun, Saitama 349-02 (JP).

(74) Agents: YAMAMOTO, Ryozo et al.; Torimoto Kogyo Building, 38, Kanda-Higashimatsushitacho, Chiyoda-ku, Tokyo 101 (JP).

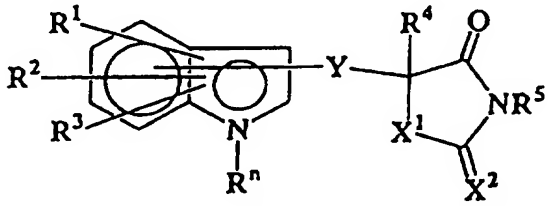
(81) Designated States: AU, CA, CN, CZ, FI, HU, KR, LT, LV, MX, NO, NZ, RO, RU, SI, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: THIAZOLIDINE AND OXAZOLIDINE INDOLES WITH HYPOCLYCEMIC ACTIVITY

(57) Abstract

An indole type thiazolidine compound of formula (I) and its salt, wherein X^1 is S or O; X^2 is S, O or NH; Y is CR^6R^7 (R^6 is a hydrogen atom or a C_1-C_7 alkyl group); R^1 is a substituent at the 2-, 3-, 4-, 5-, 6- or 7- position of an indole ring and is a C_1-C_{10} alkyl group, $-W_k$-V_l-Z (Z is a C_3-C_{10} cycloalkyl group, a C_6-C_{14} aromatic group, a C_1-C_{12} heterocyclic aromatic group, a C_1-C_6 heterocycloaliphatic group, etc., V is O, S, etc., W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and each of k and *l* is 0 or 1), -V-W-Z (V, W and Z are as defined above), -W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different), or R^1 may be a hydrogen atom when Y is bonded to the 4-, 5-, 6- or 7-position of an indole ring; each of R^2 and R^3 is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring, and is independently a hydrogen atom, a C^1-C_7 alkyl group, or the like; R^4 is a hydrogen atom or a C_1-C_7 alkyl group; R^5 is a hydrogen atom or a carboxymethyl group; and R^n is a substituent at the 1-position of an indole ring, and is a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, an alkylsulfonyl group, an arylsulfonyl group, or the like.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DESCRIPTION

THIAZOLIDINE AND OXAZOLIDINE INDOLES WITH HYPOCLYCEMIC ACTIVITY

TECHNICAL FIELD

The present invention relates to novel indole type thiazolidines having a hypoglycemic effect and aldose-reductase inhibitory activities, which are useful in medical and veterinary fields, particularly useful for preventing or treating diabetes mellitus and diabetic complications.

BACKGROUND TECHNIQUE

Heretofore, various sulfonylurea derivatives and biguanide derivatives have been widely used as oral hypoglycemic agents for lowering blood sugar levels. However, these agents had disadvantages of causing serious hypoglycemic coma and lactic acidosis revelation, and therefore every possible care must have been taken for practical use. "Chem. Pharm. Bull., vol. 30, p. 3563 (1982)", "J. Med. Chem., vol. 32, p. 421 (1989)", "J. Med. Chem., vol. 34, p. 318 (1991)", "J. Med. Chem., vol. 33, p. 1418 (1990)", Japanese Unexamined Patent Publication No. 64586/1980, and European Laid Open Patent Publications No. 177353, No. 283035, No. 283036, No. 332331, and No. 332332 disclose various thiazolidindiones which achieve a hypoglycemic effect, and these are particularly useful for treating Type II diabetes and are

noted as agents for hardly causing such hypoglycemic symptoms as caused by the above-mentioned oral hypoglycemic agents. However, although these compounds have a function of effectively lowering a blood sugar level, it is not proved that these compounds have effects for reducing or preventing various chronic symptoms caused by diabetes, such as diabetic nephropathy, diabetic cataract, diabetic retinopathy, diabetic neuropathy and the like.

Further, some of a series of indole derivatives having a thiazolidine ring or an oxazolidine ring as a partial structure, are known. For example, there is reported in Bioorg. Med. Chem. Lett., vol. 2(7), P705 (1992) that a series of 3-((4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives have cyclooxygenase and 5-lipoxygenase inhibitory activities. Arch. Pharm. (Weinheim)., vol. 304(7), P523 (1971) and European Patent No. 343643 disclose that a series of 2-((4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives have anti-inflammatory and anti-allergy activities. Japanese Examined Patent Publication No. 56175/1986 and European Laid Open Patent Publication No. 47109 disclose that a series of 3-((N-carboxymethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives have aldose-reductase inhibitory activities. Indian Drugs, vol. 22(10), P519 (1985) and J. Chem. Soc. Pak., vol. 4(1), P43 (1982) discloses a series of 3-((4-

oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives have CNS activities. Japanese Unexamined Patent Publication No. 96941/1980 discloses that a series of 3-((4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives are useful as a photographic material of silver halide. Anal. Lett., vol. 17(A13), P1447 (1984) discloses that 3-((4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole is useful as a spectroscopic analytical reagent. J. Med. Chem., vol 21 (1), P82 (1977) discloses that a series of 3-(4-oxo-2-thioxo-5-thiazolidinylmethyl)indole derivatives have anti-bacterial activities. J. Med. Chem., vol. 10(5), P852 (1967) discloses that a series of 3-((4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives have decarboxylase inhibitory activities. However, it is not known at all that these compounds have a hypoglycemic effect.

Belgian Laid Open Patent Publication No. 889758 discloses that a compound having 2,4-dioxo-5-oxazolidinyl directly bonded with an indole ring as a hypoglycemic effect on rats. However, these compounds are not actually synthesized, and their effects are not clear. Also, US Patent No. 4,738,972 and PCT Publication No. 8607056 disclose that a compound having 2,4-dioxo-5-thiazolidinyl directly bonded to the 5-position of an indoline ring has a hypoglycemic effect on ob/ob mice. However, these compounds are not actually synthesized and

their effects are not clear. European Laid Open Patent Publication No. 587377 discloses N-substituted 2- or 3-indolylmethylene-2-thioxo-4-thiazolidinone has a hypoglycemic effect on yellow obese diabetes mellitus mice, but its effect is not satisfactory.

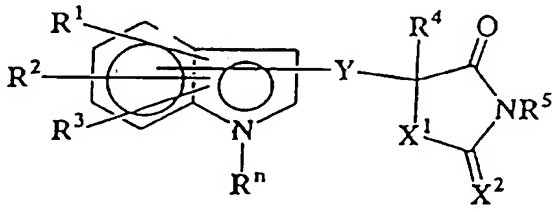
On the other hand, aldose reductase (AR) is known to be an enzyme for reducing aldoses such as glucose and galactose to polyols such as sorbitol and galactitol in a living body. It is also known that accumulation of the polyols thus produced by the enzyme in organs induces or exacerbates various diabetic complications such as diabetic retinopathy, diabetic neuropathy and diabetic nephropathy, and therefore an inhibitor against this enzyme is useful as an agent for treating these diabetic complications.

Under these circumstances, the present inventors have synthesized various thiazolidines which are not disclosed in the above-mentioned literatures, and have studied their properties. As this result, the present inventors have found compounds having excellent hypoglycemic effects and aldose-reductase inhibitory activities which were not exhibited by the above-mentioned known compounds. Thus, the present invention provides indole type thiazolidines capable of preventing or treating diabetes mellitus and diabetic complications.

DISCLOSURE OF THE INVENTION

The novel indole type thiazolidine derivatives of the

present invention are indole type thiazolidines of the following formula (I) and their salts:



(I)

wherein X^1 is S or O;

X^2 is S, O or NH;

Y is CR^6R^7 (R^6 is a hydrogen atom, a C_1-C_7 alkyl group or a C_3-C_7 cycloalkyl group, and R^7 is a hydrogen atom, a C_1-C_7 alkyl group or a C_3-C_7 cycloalkyl group, or forms a bond together with R^4);

R^1 is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring, examples of which include a C_1-C_{10} alkyl group, a C_2-C_{10} alkenyl group, a C_2-C_{10} alkynyl group, a C_1-C_{10} alkoxy group, a C_2-C_{10} alkenyloxy group, a C_1-C_{10} alkylthio group, a C_1-C_{10} monoalkylamino group or a di-C_1-C_{10} alkylamino group (each of said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyloxy, C_1-C_{10} alkylthio, C_1-C_{10} monoalkylamino and di-C_1-C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1-C_7 alkyl group), or

$-W_k-V_\ell-Z$ (Z is a C_3-C_{10} cycloalkyl group, a C_3-C_7 cycloalkenyl group, a C_6-C_{14} aromatic group, a C_1-C_{12} heterocyclic aromatic group (said heterocyclic aromatic group may contain at most 5 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and

a nitrogen atom as constituents for the heterocyclic ring), or a C_1-C_6 heterocycloaliphatic group (said heterocycloaliphatic group may contain at most 3 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring) (each of said C_3-C_{10} cycloalkyl, C_3-C_7 cycloalkenyl, C_6-C_{14} aromatic, C_1-C_{12} heterocyclic aromatic and C_1-C_6 heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group

and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group),

W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and

each of k and ℓ is 0 or 1),

-V-W-Z (V, W and Z are as defined above),

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different), or

R^1 may be a hydrogen atom when Y is bonded at the 4-, 5-, 6- or 7-position of an indole ring,

each of R^2 and R^3 is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group (said C_1-C_7 alkyl and C_3-C_7 cycloalkyl groups may be substituted with a hydroxyl group), a C_1-C_7 alkyloxy group, a benzyloxy group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group, a pyrimidinyl group, a pyridazinyl group, a furanyl group, a thienyl group, a pyrrolyl group, a pyrazolyl group, an imidazolyl group, a pyranyl group, a quinolyl group, a benzoxazolyl group, a benzothiazolyl group or a benzimidazolyl group (each of said phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,

imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl and benzimidazolyl groups may be substituted with at most 5 substituents selected from the group consisting of a hydroxyl group, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group and a halogen atom), a hydroxyl group or halogen atom;

R^4 is a hydrogen atom or a C_1-C_7 alkyl group, or forms a bond together with R^7;

R^5 is a hydrogen atom or a carboxymethyl group; and

R^n is a substituent at the 1-positon of an indole ring, examples of which include a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_4 alkoxymethyl group, an aryloxymethyl group, a C_1-C_4 alkylaminomethyl group, a substituted acetamidemethyl group, a substituted thiomethyl group, a carboxyl group, a C_1-C_7 acyl group, an arylcarbonyl group, a C_1-C_4 alkoxycarbonyl group, an aryloxycarbonyl group, a C_1-C_4 alkylaminocarbonyl group, an arylaminocarbonyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkoxyalkyloxy group, a trialkylsilyl group, a trialkylarylsilyl group, an alkylsulfonyl group or an arylsulfonyl group.

The substituents of the compound of the formula (I) of the present invention will be explained with reference to typical examples, but it should be understood that the scope of the present invention is by no means limited by these examples.

Each substituent in the formula (I) will be

specifically described hereinafter.

In the definition of R^1:

R^1 is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position, preferably at the 2- or 5-position of an indole ring.

The C_1-C_{10} alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, 1-pentyl, 2-pentyl, 3-pentyl, i-pentyl, neo-pentyl, t-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-methyl-1-ethyl-n-pentyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 3,3-dimethyl-n-butyl, 1-heptyl, 2-heptyl, 1-ethyl-1,2-dimethyl-n-propyl, 1-ethyl-2,2-dimethyl-n-propyl, 1-octyl, 3-octyl, 4-methyl-3-n-heptyl, 6-methyl-2-n-heptyl, 2-propyl-1-n-heptyl, 2,4,4-trimethyl-1-n-pentyl, 1-nonyl, 2-nonyl, 2,6-dimethyl-4-n-heptyl, 3-ethyl-2,2-dimethyl-3-n-pentyl, 3,5,5-trimethyl-1-n-hexyl, 1-decyl, 2-decyl, 4-decyl, 3,7-dimethyl-1-n-octyl, and 3,7-dimethyl-3-n-octyl. Preferred is a C_4-C_{10} alkyl group which includes, for example, n-butyl, i-butyl, s-butyl, t-butyl, 1-pentyl, 2-pentyl, 3-pentyl, i-pentyl, neo-pentyl, t-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-methyl-1-ethyl-n-pentyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 3,3-dimethyl-n-butyl, 1-heptyl, 2-heptyl, 1-ethyl-1,2-dimethyl-n-propyl, 1-ethyl-2,2-dimethyl-n-propyl, 1-octyl, 3-octyl, 4-methyl-3-n-heptyl, 6-methyl-2-n-heptyl, 2-propyl-1-n-heptyl, 2,4,4-trimethyl-1-n-pentyl, 1-nonyl, 2-nonyl, 2,6-dimethyl-4-n-

heptyl, 3-ethyl-2,2-dimethyl-3-n-pentyl, 3,5,5-trimethyl-1-n-hexyl, 1-decyl, 2-decyl, 4-decyl, 3,7-dimethyl-1-n-octyl and 3,7-dimethyl-3-n-octyl. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The C_2-C_{10} alkenyl group includes, for example, ethenyl, 1-propenyl, 2-propenyl, 1-methylvinyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-ethyl-2-vinyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl, 2,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2,4-hexadienyl, 1-methyl-1-pentenyl, 1-heptenyl, 1-octenyl, 1-nonenyl and 1-decenyl. Preferred is a C_5-C_{10} alkenyl group which includes, for example, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl, 2,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2,4-hexadienyl, 1-methyl-1-pentenyl, 1-heptenyl, 1-octenyl, 1-nonenyl and 1-decenyl. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The C_2-C_{10} alkynyl group includes, for example, ethynyl,1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-

butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl, 1-nonynyl, and 1-decynyl. Preferred is a C_5-C_{10} alkynyl group which includes, for example, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl, 1-nonynyl and 1-decynyl. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The C_1-C_{10} alkoxy group includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy and decyloxy. Preferred is a C_4-C_{10} alkoxy group which includes, for example, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy and decyloxy. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The C_2-C_{10} alkenyloxy group includes, for example, ethenyloxy, 1-propenyloxy, 2-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 1-pentenyloxy, 2-pentenyloxy, 3-pentenyloxy, 4-pentenyloxy, 2,4-pentadienyloxy, 1-hexenyloxy, 2-hexenyloxy, 3-hexenyloxy, 4-hexenyloxy, 5-hexenyloxy, 2,4-hexadienyloxy, 1-heptenyloxy, 1-octenyloxy, 1-nonenyloxy and 1-decenyloxy. Preferred is a C_5-C_{10} alkenyloxy which includes, for example, 1-pentenyloxy, 2-pentenyloxy, 3-pentenyloxy, 4-pentenyloxy, 2,4-pentadienyloxy, 1-hexenyloxy, 2-hexenyloxy, 3-

hexenyloxy, 4-hexenyloxy, 5-hexenyloxy, 2,4-hexadienyloxy, 1-heptenyloxy, 1-octenyloxy, 1-nonenyloxy and 1-decenyloxy. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The C_1-C_{10} alkylthio group includes, for example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-butylthio, t-butylthio, pentylthio, hexylthio, heptylthio, octylthio, nonylthio and decylthio. Preferred is a C_5-C_{10} alkylthio which includes, for example, pentylthio, hexylthio, heptylthio, octylthio, nonylthio and decylthio. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The C_1-C_{10} monoalkylamino group includes, for example, methylamino, ethylamino, n-propylamino, i-propylamino, n-butylamino, i-butylamino, s-butylamino, t-butylamino, pentylamino, hexylamino, heptylamino, octylamino, nonylamino and decylamino. Preferred is a C_5-C_{10} monoalkylamino group which includes, for example, pentylamino, hexylamino, heptylamino, octylamino, nonylamino and decylamino. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The di-C_1-C_{10} alkylamino group includes, for example, dimethylamino, diethylamino, di-n-propylamino, di-i-propylamino, d-n-hexylamino, N-methyl-N-n-pentylamino, N-methyl-N-n-hexylamino, N-methyl-N-n-heptylamino, N-methyl-N-n-octylamino, N-methyl-N-n-nonylamino, and N-methyl-N-n-decylamino. Preferred are, for example, N-

methyl-N-n-pentylamino, N-methyl-N-n-hexylamino, N-methyl-N-n-heptylamino, N-methyl-N-n-octylamino, N-methyl-N-n-nonylamino, and N-methyl-N-n-decylamino. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

In the definition of Z:

The C_3-C_{10} cycloalkyl group includes, for example, cyclopropyl, 1-methyl-cyclopropyl, 2-methyl-cyclopropyl, 4-methyl-cyclohexyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 1-adamantyl, and 2-adamantyl. Preferred is a C_6-C_{10} cycloalkyl group which includes, for example, cyclohexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 1-adamantyl and 2-adamantyl. Each group may have at most 5 substituents (the substituents may, for example, be a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy

group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C_3-C_7 cycloalkenyl group includes, for example, cyclohexenyl (said cyclohexenyl includes 1-cyclohexenyl, 2-cyclohexenyl, and 3-cyclohexenyl), cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl, and 2,5-bicyclo[2.2.1]heptadienyl. Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl

group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C_6-C_{14} aromatic group includes, for example, phenyl, naphthyl (said naphthyl includes α-naphthyl, and β-naphthyl), indenyl (said indenyl includes 1-indenyl, 2-indenyl, 3-indenyl, 4-indenyl, 5-indenyl, 6-indenyl, and 7-indenyl), indanyl (said indanyl includes 1-indanyl, 2-indanyl, 4-indanyl, and 5-indanyl), and fluorenyl (said fluorenyl includes 1-fluorenyl, 2-fluorenyl, 3-fluorenyl, 4-fluorenyl, and 9-fluorenyl). Preferred is a C_6-C_{14} aromatic group which includes, for example, phenyl, naphthyl (said naphthyl includes α-naphthyl, and β-naphthyl), and fluorenyl (said fluorenyl includes 1-fluorenyl, 2-fluorenyl, 3-fluorenyl, 4-fluorenyl, and 9-fluorenyl). Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom,

a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C_1-C_{12} heterocyclic aromatic group is a heterocyclic group having a 5-15 membered monocyclic or condensed ring containing at most 5 hetero-atoms in the ring, selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom. Examples of the

heterocyclic aromatic group include furyl (said furyl includes 2-furyl, and 3-furyl), thienyl (said thienyl includes 2-thienyl, and 3-thienyl), pyrrolyl (said pyrrolyl includes 1-pyrrolyl, 2-pyrrolyl, and 3-pyrrolyl), oxazolyl (said oxazolyl includes 2-oxazolyl, 4-oxazolyl, and 5-oxazolyl), thiazolyl (said thiazolyl includes 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl), isoxazolyl (said isoxazolyl includes 3-isoxazolyl, 4-isoxazolyl, and 5-isoxazolyl), isothiazolyl (said isothiazolyl includes 3-isothiazolyl, 4-isothiazolyl, and 5-isothiazolyl), furazanyl (said furazanyl includes 3-furazanyl), pyrazolyl (said pyrazolyl includes 1-pyrazolyl, 3-pyrazolyl, and 4-pyrazolyl), oxopyrazolyl (said oxopyrazolyl includes 3-oxopyrazol-1-yl, 3-oxopyrazol-2-yl, 3-oxopyrazol-3-yl, 3-oxopyrazol-4-yl, and 4-oxopyrazol-3-yl), imidazolyl (said imidazolyl includes 1-imidazolyl, 2-imidazolyl, and 4-imidazolyl), oxoimidazolyl (said oxoimidazolyl includes 2-oxoimidazol-1-yl, and 2-oxoimidazol-4-yl), triazolyl (said triazolyl includes 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, and 1,2,4-triazol-4-yl), triazolonyl (said triazolonyl includes 1,2,4(2H,4H)-triazol-3-on-2-yl, 1,2,4-(2H,4H)-triazol-3-on-4-yl, 1,2,4(2H,4H)-triazol-3-on-5-yl, 1,2,4(1H,2H)-triazol-3-on-1-yl, 1,2,4(1H,2H)-triazol-3-on-2-yl, and 1,2,4(1H,2H)-triazol-3-on-5-yl), tetrazolyl (said tetrazolyl includes 1-tetrazolyl, 2-tetrazolyl, and

5-tetrazolyl), pyranyl (said pyranyl includes 2-pyranyl, 3-pyranyl, and 4-pyranyl), pyridyl (said pyridyl includes 2-pyridyl, 3-pyridyl, and 4-pyridyl), pyridonyl (said pyridonyl includes 2-pyridon-1-yl, 2-pyridon-3-yl, 2-pyridon-4-yl, 2-pyridon-5-yl, 2-pyridon-6-yl, 4-pyridon-1-yl, 4-pyridon-2-yl, and 4-pyridon-3-yl), pyridazinyl (said pyridazinyl includes 3-pyridazinyl, and 4-pyridazinyl), pyridazinonyl (said pyridazinonyl includes 3(2H)-pyridazinon-2-yl, 3(2H)-pyridazinon-4-yl, 3(2H)-pyridazinon-5-yl, 3(2H)-pyridazinon-6-yl, 4(1H)-pyridazinon-1-yl, 4(1H)-pyridazinon-3-yl, 4(1H)-pyridazinon-5-yl, and 4(1H)-pyridazinon-6-yl), pyrimidinyl (said pyrimidinyl includes 2-pyrimidinyl, 4-pyrimidinyl, and 5-pyrimidinyl), pyrimidinonyl (said pyrimidinonyl includes (2(1H)-pyrimidinon-1-yl, 2(1H)-pyrimidinon-4-yl, 2(1H)-pyrimidinon-5-yl, 2(1H)-pyrimidinon-6-yl, 4(3H)-pyrimidinon-2-yl, 4(3H)-pyrimidinon-3-yl, 4(3H)-pyrimidinon-5-yl, 4(3H)-pyrimidinon-6-yl, 4(1H)-pyrimidinon-1-yl, 4(1H)-pyrimidinon-2-yl, 4(1H)-pyrimidinon-5-yl, and 4(1H)-pyrimidinon-6-yl), pyrazinyl (said pyrazinyl includes 2-pyrazinyl, 2(1H)-pyrazin-1-yl, 2(1H)-pyrazin-3-yl, 2(1H)-pyrazin-5-yl, and 2(1H)-pyrazin-6-yl), triazinyl (said triazinyl includes 1,2,3-triazin-4-yl, 1,2,3-triazin-5-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, and 1,2,4-triazin-6-yl), tetrazinyl (said tetrazinyl includes 1,2,3,4-tetrazin-5-yl, and 1,2,4,5-tetrazin-3-yl),

indolyl (said indolyl includes 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, and 7-indolyl), quinolyl (said quinolyl includes 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, and 8-quinolyl), quinolonyl (said quinolonyl includes 2-quinolon-1-yl, 2-quinolon-3-yl, 2-quinolon-4-yl, 2-quinolon-5-yl, 2-quinolon-6-yl, 2-quinolon-7-yl, 2-quinolon-8-yl, 4-quinolon-1-yl, 4-quinolon-2-yl, 4-quinolon-3-yl, 4-quinolon-5-yl, 4-quinolon-6-yl, 4-quinolon-7-yl, and 4-quinolon-8-yl), benzofuranyl (said benzofuranyl includes 2-benzofuranyl, 3-benzofuranyl, 4-benzofuranyl, 5-benzofuranyl, 6-benzofuranyl, and 7-benzofuranyl), benzothienyl (said benzothienyl includes 2-benzothienyl, 3-benzothienyl, 4-benzothienyl, 5-benzothienyl, 6-benzothienyl, and 7-benzothienyl), isoquinolyl (said isoquinolyl includes 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, and 8-isoquinolyl), isoquinolonyl (said isoquinolonyl includes 1-isoquinolon-2-yl, 1-isoquinolon-3-yl, 1-isoquinolon-4-yl, 1-isoquinolon-5-yl, 1-isoquinolon-6-yl, 1-isoquinolon-7-yl, 1-isoquinolon-8-yl, 3-isoquinolon-2-yl, 3-isoquinolon-4-yl, 3-isoquinolon-5-yl, 3-isoquinolon-6-yl, 3-isoquinolon-7-yl, and 3-isoquinolon-8-yl), benzoxazolyl (said benzoxazolyl includes 2-benzoxazolyl, 4-benzoxazolyl, 5-benzoxazolyl, 6-benzoxazolyl, and 7-benzoxazolyl), benzothiazolyl (said benzothiazolyl includes 2-benzothiazolyl, 4-

benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, and 7-benzothiazolyl), benzopyrazolyl (said benzopyrazolyl includes 1-benzopyrazolyl, 2-benzopyrazolyl, 3-benzopyrazolyl, 4-benzopyrazolyl, 5-benzopyrazolyl, 6-benzopyrazolyl, and 7-benzopyrazolyl), benzimidazolyl (said benzimidazolyl includes 1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, and 5-benzimidazolyl), benzotriazolyl (said benzotriazolyl includes 1-benzotriazolyl, 4-benzotriazolyl, and 5-benzotriazolyl), benzopyranyl (said benzopyranyl includes 2-benzopyranyl, 3-benzopyranyl, 4-benzopyranyl, 5-benzopyranyl, 6-benzopyranyl, 7-benzopyranyl, and 8-benzopyranyl), indolizinyl (said indolizinyl includes 1-indolizinyl, 2-indolizinyl, 3-indolizinyl, 5-indolizinyl, 6-indolizinyl, 7-indolizinyl, and 8-indolizinyl), purinyl (said purinyl includes 2-purinyl, 6-purinyl, 7-purinyl, and 8-purinyl), phthalazinyl (said phthalazinyl includes 1-phthalazinyl, 5-phthalazinyl, and 6-phthalazinyl), oxophthalazinyl (said oxophthalazinyl includes 1-oxophthalazin-2-yl, 1-oxophthalazin-4-yl, 1-oxophthalazin-5-yl, 1-oxophthalazin-6-yl, 1-oxophthalazin-7-yl, and 1-oxophthalazin-8-yl), naphthyridinyl (said naphthyridinyl includes 2-naphthyridinyl, 3-naphthyridinyl, and 4-naphthyridinyl), quinoxalinyl (said quinoxalinyl includes 2-quinoxalinyl, 5-quinoxalinyl, and 6-quinoxalinyl), quinazolinyl (said quinazolinyl includes 2-quinazolinyl, 4-quinazolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-

quinazolinyl, and 8-quinazolinyl), cinnolinyl (said cinnolinyl includes 3-cinnolinyl, 4-cinnolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, and 8-cinnolinyl), benzodioxolyl (said benzodioxolyl includes 1,3-benzodioxol-4-yl, and 1,3-benzodioxol-5-yl), benzodioxanyl (said benzodioxanyl includes 1,4-benzodioxan-2-yl, 1,4-benzodioxan-5-yl, and 1,4-benzodioxan-6-yl), oxonaphthalenyl (said oxonaphthalenyl includes 1,4-oxonaphthalen-2-yl, 1,4-oxonaphthalen-5-yl, and 1,4-oxonaphthalen-6-yl), 2,3-dihydrobenzofuranyl (said 2,3-dihydrobenzofuranyl includes 2,3-dihydro-4-benzofuranyl, 2,3-dihydro-5-benzofuranyl, 2,3-dihydro-6-benzofuranyl, and 2,3-dihydro-7-benzofuranyl), benzothiazinyl (said benzothiazinyl includes 1,4-benzothiazin-2-yl, 1,4-benzothiazin-3-yl, 1,4-benzothiazin-4-yl, 1,4-benzothiazin-5-yl, 1,4-benzothiazin-6-yl, 1,4-benzothiazin-7-yl, and 1,4-benzothiazin-8-yl), pteridinyl (said pteridinyl includes 2-pteridinyl, 4-pteridinyl, 6-pteridinyl, and 7-pteridinyl), pyrazolo[1,5-a]pyrimidinyl (said pyrazolo[1,5-a]pyrimidinyl includes pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-3-yl, pyrazolo[1,5-a]pyrimidin-5-yl, pyrazolo[1,5-a]pyrimidin-6-yl, and pyrazolo[1,5-a]pyrimidin-7-yl), pyrazolo[5,1-c][1,2,4]triazinyl (said pyrazolo[5,1-c][1,2,4]triazinyl includes pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrazolo[5,1-c][1,2,4]triazin-4-yl, pyrazolo[5,1-

c][1,2,4]triazin-7-yl, and pyrazolo[5,1-c][1,2,4]triazin-8-yl), thiazolo[3,2-b]triazolyl (said thiazolo[3,2-b]triazolyl includes thiazolo[3,2-b]triazol-2-yl, thiazolo[3,2-b]triazol-5-yl, and thiazolo[3,2-b]triazol-6-yl), benzopyrano[2,3-b]pyridyl (said benzopyrano[2,3-b]pyridyl includes benzopyrano[2,3-b]pyridin-2-yl, benzopyrano[2,3-b]pyridin-3-yl, benzopyrano[2,3-b]pyridin-4-yl, benzopyrano[2,3-b]pyridin-5-yl, benzopyrano[2,3-b]pyridin-6-yl, benzopyrano[2,3-b]pyridin-7-yl, benzopyrano[2,3-b]pyridin-8-yl, and benzopyrano[2,3-b]pyridin-9-yl), 5H-benzopyrano[2,3-b]pyridonyl (said 5H-benzopyrano[2,3-b]pyridonyl includes 5H-benzopyrano[2,3-b]pyridin-5-on-2-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-3-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-4-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-6-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-7-yl, and 5H-benzopyrano[2,3-b]pyridin-5-on-8-yl), xanthenyl (said xanthenyl includes 1-xanthenyl, 2-xanthenyl, 3-xanthenyl, 4-xanthenyl, and 9-xanthenyl), phenoxathiinyl (said phenoxathiinyl includes 1-phenoxathiinyl, 2-phenoxathiinyl, 3-phenoxathiinyl, and 4-phenoxathiinyl), carbazolyl (said carbazolyl includes 1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl, and 9-carbazolyl), acridinyl (said acridinyl includes 1-acridinyl, 2-acridinyl, 3-acridinyl, 4-acridinyl, and 9-acridinyl), phenazinyl (said phenazinyl includes 1-phenazinyl, 2-phenazinyl, 3-phenazinyl, and 4-

phenazinyl), phenothiazinyl (said phenothiazinyl includes 1-phenothiazinyl, 2-phenothiazinyl, 3-phenothiazinyl, 4-phenothiazinyl, and 10-phenothiazinyl), phenoxazinyl (said phenoxazinyl includes 1-phenoxazinyl, 2-phenoxazinyl, 3-phenoxazinyl, 4-phenoxazinyl, and 10-phenoxazinyl), and thianthrenyl (said thianthrenyl includes 1-thianthrenyl, 2-thianthrenyl, 3-thianthrenyl, 4-thianthrenyl, 6-thianthrenyl, 7-thianthrenyl, 8-thianthrenyl, and 9-thianthrenyl). Preferred examples of the C_1-C_{12} heterocyclic aromatic group include furyl (said furyl includes 2-furyl, and 3-furyl), thienyl (said thienyl includes 2-thienyl, and 3-thienyl), pyrrolyl (said pyrrolyl includes 1-pyrrolyl, 2-pyrrolyl, and 3-pyrrolyl), oxazolyl (said oxazolyl includes 2-oxazolyl, 4-oxazolyl, and 5-oxazolyl), thiazolyl (said thiazolyl includes 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl), isoxazolyl (said isoxazolyl includes 3-isoxazolyl, 4-isoxazolyl, and 5-isoxazolyl), isothiazolyl (said isothiazolyl includes 3-isothiazolyl, 4-isothiazolyl, and 5-isothiazolyl), imidazolyl (said imidazolyl includes 1-imidazolyl, 2-imidazolyl, and 4-imidazolyl), pyridyl (said pyridyl includes 2-pyridyl, 3-pyridyl, and 4-pyridyl), pyridazinyl (said pyridazinyl includes 3-pyridazinyl, and 4-pyridazinyl), pyridazinonyl (said pyridazinonyl includes 3(2H)-pyridazinon-2-yl, 3(2H)-pyridazinon-4-yl, 3(2H)-pyridazinon-5-yl, and 3(2H)-pyridazinon-6-yl), pyrimidinyl (said pyrimidinyl includes

2-pyrimidinyl, 4-pyrimidinyl, and 5-pyrimidinyl), pyrazinyl (said pyrazinyl includes 2-pyrazinyl), indolyl (said indolyl includes 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, and 7-indolyl), quinolyl (said quinolyl includes 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, and 8-quinolyl), benzoxazolyl (said benzoxazolyl includes 2-benzoxazolyl, 4-benzoxazolyl, 5-benzoxazolyl, 6-benzoxazolyl, and 7-benzoxazolyl), benzothiazolyl (said benzothiazolyl includes 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, and 7-benzothiazolyl), benzimidazolyl (said benzimidazolyl includes 1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, and 5-benzimidazolyl), phthalazinyl (said phthalazinyl includes 1-phthalazinyl, 5-phthalazinyl, and 6-phthalazinyl), quinoxalinyl (said quinoxalinyl includes 2-quinoxalinyl, 5-quinoxalinyl, and 6-quinoxalinyl), benzodioxolyl (said benzodioxolyl includes 1,3-benzodioxol-4-yl, and 1,3-benzodioxol-5-yl), benzothiazinyl (said benzothiazinyl includes 1,4-benzothiazin-2-yl, 1,4-benzothiazin-3-yl, 1,4-benzothiazin-4-yl, 1,4-benzothiazin-5-yl, 1,4-benzothiazin-6-yl, 1,4-benzothiazin-7-yl, and 1,4-benzothiazin-8-yl), pyrazolo[1,5-a]pyrimidinyl (said pyrazolo[1,5-a]pyrimidinyl includes pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-3-yl, pyrazolo[1,5-a]pyrimidin-5-yl, pyrazolo[1,5-a]pyrimidin-

6-yl, and pyrazolo[1,5-a]pyrimidin-7-yl), pyrazolo[5,1-c][1,2,4]triazinyl (said pyrazolo[5,1-c][1,2,4]triazinyl includes pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrazolo[5,1-c][1,2,4]triazin-4-yl, pyrazolo[5,1-c][1,2,4]triazin-7-yl, and pyrazolo[5,1-c][1,2,4]triazin-8-yl), thiazolo[3,2-b]triazolyl (said thiazolo[3,2-b]triazolyl includes thiazolo[3,2-b]triazol-2-yl, thiazolo[3,2-b]triazol-5-yl, and thiazolo[3,2-b]triazol-6-yl), and benzopyrano[2,3-b]pyridyl (said benzopyrano[2,3-b]pyridyl includes benzopyrano[2,3-b]pyridin-2-yl, benzopyrano[2,3-b]pyridin-3-yl, benzopyrano[2,3-b]pyridin-4-yl, benzopyrano[2,3-b]pyridin-5-yl, benzopyrano[2,3-b]pyridin-6-yl, benzopyrano[2,3-b]pyridin-7-yl, benzopyrano[2,3-b]pyridin-8-yl, and benzopyrano[2,3-b]pyridin-9-yl). Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a

tri-C_1-C_7-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C_1-C_6 heterocycloaliphatic group is a heterocyclic group having a 3-8 membered monocyclic or condensed dicyclic ring containing at most 3 hetero-atoms in the ring, selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom. Examples of the heterocycloaliphatic group include piperidyl (said piperidyl includes 1-piperidyl, 2-piperidyl, 3-piperidyl, and 4-piperidyl), pyrrolidinyl (said pyrrolidinyl includes 1-pyrrolidinyl, 2-pyrrolidinyl, and 3-pyrrolidinyl), imidazolidinyl (said imidazolidinyl includes 1-imidazolidinyl, 2-imidazolidinyl, and 4-imidazolidinyl), pyrazolidinyl (said pyrazolidinyl includes 1-pyrazolidinyl, 3-pyrazolidinyl, and 4-pyrazolidinyl), morpholinyl (said morpholinyl includes 2-morpholinyl, 3-morpholinyl, and 4-morpholinyl), and

tetrahydrofuranyl (said tetrahydrofuranyl includes 2-tetrahydrofuranyl, and 3-tetrahydrofuranyl). Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

In the definitions of R^a, R^b and R^c:

The C_1-C_7 alkyl group includes, for example, methyl,

ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl, and n-heptyl. Preferred are methyl, ethyl and n-propyl. Each group may be substituted with a hydroxyl group.

The C_3-C_7 cycloalkyl group includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl, and bicyclo[3.1.1]heptyl. Preferred are cyclopropyl and cyclohexyl. Each group may be substituted by a hydroxyl group.

The C_3-C_7 cycloalkenyl group includes, for example, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl and 2,5-bicyclo[2.2.1]heptadienyl. Each group may be substituted by a hydroxyl group.

The C_1-C_7 alkoxy group includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy and heptyloxy.

The C_1-C_7 alkylthio group includes, for example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-buthylthio, t-butylthio, pentylthio, hexylthio and heptylthio.

The tri-C_1-C_7-alkylsilyloxy group includes, for example, trimethylsilyloxy, triethylsilyloxy, triisopropylsilyloxy, diethylisopropylsilyloxy, dimethylisopropylsilyloxy, di-t-butylmethylsilyloxy,

isopropyldimethylsilyloxy, t-butyldimethylsilyloxy, thexyldimethylsilyloxy or the like, preferably t-butyldimethylsilyloxy or the like.

The naphthyl group includes an α-naphthyl group, a β-naphthyl group. The furanyl group includes a 2-furanyl group and a 3-furanyl group. The thienyl group includes a 2-thienyl group and a 3-thienyl group. The imidazolyl group includes a 1-imidazolyl group, a 2-imidazolyl group and a 4-imidazolyl group. The pyridyl group includes a 2-pyridyl group and a 3-pyridyl group and a 4-pyridyl group. Each groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group.

The phenyl and the benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group.

The C_1-C_3 alkoxycarbonyl group includes, for example, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl and i-propoxycarbonyl.

The halogen atom includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. Preferred are a

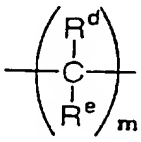
fluorine atom, a chlorine atom and a bromine atom.

V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or C_1-C_3 alkyl (which may, for example, be methyl, ethyl, n-propyl or i-propyl, preferably methyl)). It is preferably S, SO, SO_2 or NR^8.

W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3, preferably at most 2, of hydroxyl, oxo and C_1-C_7 alkyl groups.

The C_1-C_7 alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl and n-heptyl. Preferred may, for example, be methyl.

W is preferably



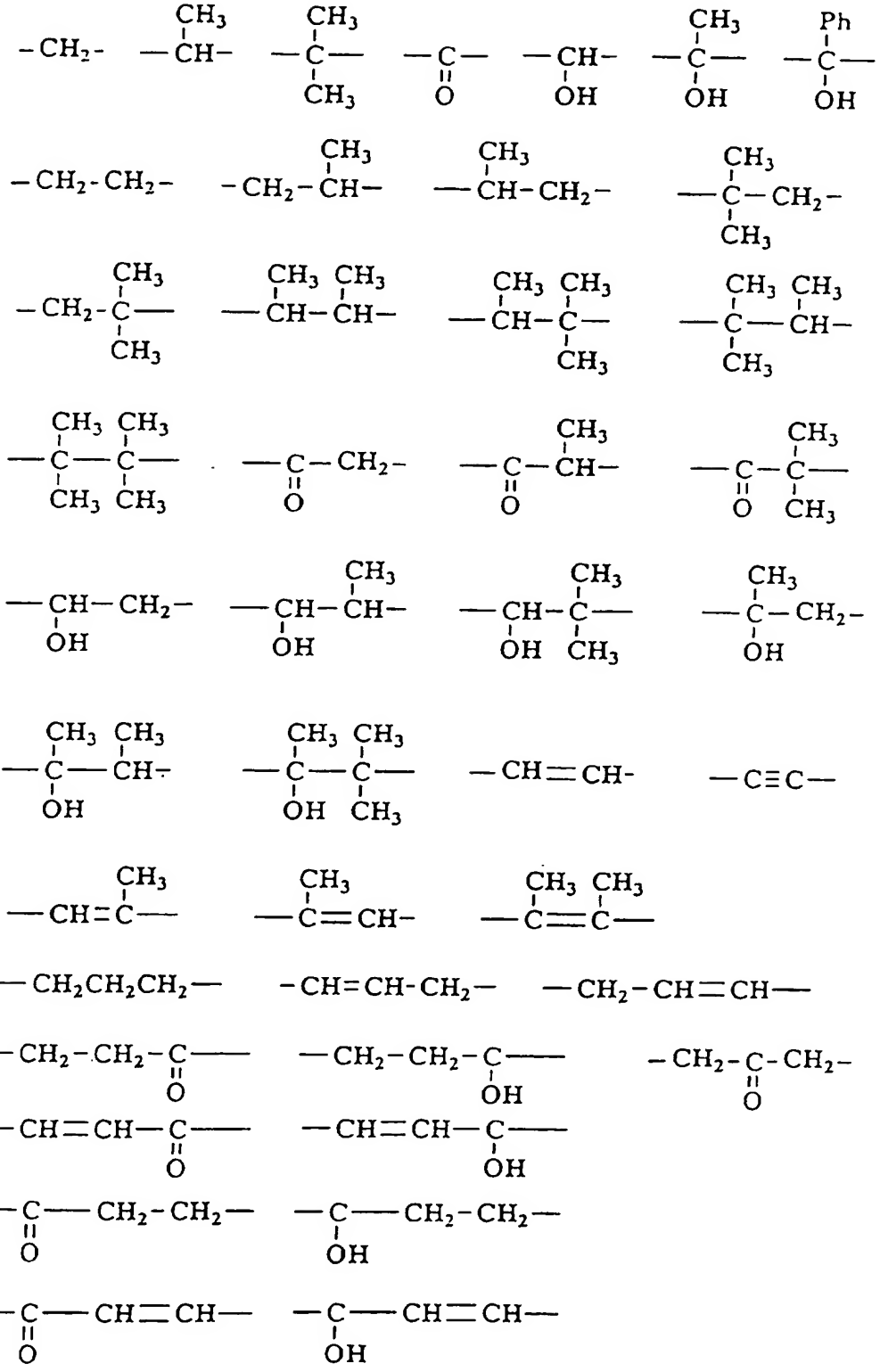
wherein m is from 1 to 5, and each of R^d and R^e is a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to N are not hydroxyl groups and provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group).

R^1 may be $-W_k-V_\ell-Z$, -V-W-Z or -W-V-W-Z in addition to

the one mentioned above.

$-W_k-V_\ell-Z$ may, for example, be -W-Z, -V-Z or -W-V-Z.

Preferable examples of -W- in the above -W-Z are illustrated below.



Also, preferable examples of -V- in the above -V-Z include S, SO and SO_2.

Also, preferable examples of -W-V- in the above -W-V-Z include $-CO-NR^8-$ (R^8 is a hydrogen atom or a C_1-C_3 alkyl group (e.g. methyl, ethyl, n-propyl or i-propyl, preferably methyl)).

Also, preferable examples of -V-W- in the above -V-W-Z include $-O-(CH_2)_n-$(n is from 1 to 5).

Also, preferable examples of -W-V-W- in the above -W-V-W-Z include $-(CH_2)_n-NR^8-CO-$ (n is from 1 to 5, R^8 is a hydrogen atom or a C_1-C_3 alkyl group (e.g. methyl, ethyl, n-propyl or i-propyl, preferably methyl)).

Each of R^2 and R^3 independently is a hydrogen atom, a C_1-C_7 alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl, and said C_1-C_7 alkyl group may be substituted with at most two hydroxyl groups, preferably one hydroxyl group), a C_3-C_7 cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl or bicyclo[3.1.1]heptyl, preferably cyclopropyl or cyclohexyl, and said C_3-C_7 cycloalkyl group may be substituted with at most 2 hydroxyl group, preferably one hydroxyl group), a C_1-C_7 alkoxy group (which may, for example, be methoxy, ethoxy n-propoxy, i-propoxy, n-

butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy or heptyloxy, preferably methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy or t-butoxy), a benzyloxy group, a phenyl group, a naphthyl group (which may be an α-naphthyl group, or a β-naphthyl group), a benzyl group, a pyridyl group (which may, for example, be a 2-pyridyl group, a 3-pyridyl group or a 4-pyridyl group, preferably a 2-pyridyl group), a pyrimidinyl group (which may, for example, be a 2-pyrimidinyl group, a 4-pyrimidinyl group or a 5-pyrimidinyl group), a pyridazinyl group (which may, for example, be a 3-pyridazinyl group or a 4-pyridazinyl group), a furanyl group (which may, for example, be a 2-furanyl group or a 3-furanyl group), a thienyl group (which may, for example, be a 2-thienyl group or a 3-thienyl group), a pyrrolyl group (which may, for example, be a 1-pyrrolyl group, a 2-pyrrolyl group or a 3-pyrrolyl group), a pyrazolyl group (which may, for example, be a 1-pyrazolyl group, a 3-pyrazolyl group or a 4-pyrazolyl group), an imidazolyl group (which may, for example, be a 1-imidazolyl group, a 2-imidazolyl group or a 4-imidazolyl group), a pyranyl group (which may, for example, be 2-pyranyl, 3-pyranyl or 4-pyranyl, preferably 2-pyranyl), a quinolyl group (which may, for example, be 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl or 8-quinolyl, preferably 2-quinolyl), a benzoxazolyl group (which may, for example, be a 2-benzoxalyl group, a

4-benzoxazolyl group, a 5-benzoxazolyl group, a 6-benzoxazolyl group or a 7-benzoxazolyl group, preferably a 2-benzoxazolyl group), a benzothiazolyl group (which may, for example, be a 2-benzothiazolyl group, a 4-benzothiazolyl group, a 5-benzothiazolyl group, a 6-benzothiazolyl group or a 7-benzothiazolyl group, preferably a 2-benzothiazolyl group), or a benzimidazolyl group (which may, for example, be a 1-benzimidazolyl group, a 2-benzimidazolyl group, a 4-benzimidazolyl group or a 5-benzimidazolyl group, preferably a 2-benzimidazolyl group).

When R^2 or R^3 is a phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl, or benzimidazolyl group, the substituents for such a phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl group may be as follows.

The C_1-C_7 alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl and n-heptyl. Preferred may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl.

The C_1-C_7 alkoxy group includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy and

heptyloxy. Preferred may, for example, be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy or t-butoxy.

The halogen atom may, for example, be a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, preferably, a fluorine atom, a chlorine atom or a bromine atom.

R^4 is a hydrogen atom or a C_1-C_7 alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl), or forms a bond together with R^7. It is preferably a hydrogen atom or a methyl group, or forms a bond together with R^7. More preferably, it is a hydrogen atom, or forms a bond together with R^7.

R^5 is a hydrogen atom or a carboxymethyl group, preferably a hydrogen atom.

R^n is a substituent at the 1-position of an indole ring, and is a hydrogen atom, a C_1-C_7 alkyl group (such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl and n-heptyl, preferably a C_1-C_3 alkyl group), a C_3-C_7 cycloalkyl group (such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, preferably cyclopropyl), a C_1-C_4 alkoxymethyl group (such as MOM: methoxymethyl, MEM: 2-methoxyethoxymethyl, ethoxymethyl, n-propoxymethyl, i-propoxymethyl, n-butoxymethyl, iBM: isobutyloxymethyl,

BUM: t-butoxymethyl, POM: pivaloyloxymethyl and SEM: trimethylsilylethoxymethyl, preferably a C_1-C_2 alkoxy methyl group), an aryloxymethyl group (such as BOM: benzyloxymethyl, PMBM: p-methoxybenzyloxymethyl and p-AOM: p-anisyloxymethyl, preferably a benzyloxymethyl group), a C_1-C_4 alkylaminomethyl group (such as dimethylaminomethyl), a substituted acetamidemethyl group (such as Acm: acetamidemethyl and Tacm: trimethylacetamidemethyl), a substituted thiomethyl group (such as MTM: methylthiomethyl, PTM: phenylthiomethyl and Btm: benzylthiomethyl), a carboxyl group, a C_1-C_7 acyl group (such as formyl, acetyl, fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, propionyl, Pv: pivaloyl and tigloyl), an arylcarbonyl group (such as benzoyl, benzoylformyl, benzoylpropionyl and phenylpropionyl), a C_1-C_4 alkoxycarbonyl group (such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, i-butoxycarbonyl, BOC: t-butoxycarbonyl, AOC: t-amyloxycarbonyl, VOC: vinyloxycarbonyl, AOC: allyloxycarbonyl, Teoc: 2-(trimethylsilyl)ethoxycarbonyl, and Troc: 2,2,2-trichloroethoxycarbonyl, preferably methoxycarbonyl), an aryloxycarbonyl group (such as Z: benzyloxycarbonyl, p-nitrobenzyloxycarbonyl and MOZ: p-methoxybenzyloxycarbonyl), a C_1-C_4 alkylaminocarbonyl group (such as methylcarbamoyl, Ec: ethylcarbamoyl and n-propylcarbamoyl), an arylaminocarbonyl group (such as

phenylcarbamoyl), a C_1-C_7 alkoxy group (such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentoxy, n-hexyloxy and n-heptyloxy, preferably a C_1-C_3 alkoxy group), a C_1-C_7 alkoxyalkyloxy group (such as MOMO: methoxymethyloxy, MEMO: methoxyethyloxymethyloxy and BOMO: benzyloxymethyloxy), a trialkylsilyl group (such as TMS: trimethylsilyl, TES: triethylsilyl, TIPS: triisopropylsilyl, DEIPS: diethylisopropylsilyl, DMIPS: dimethylisopropylsilyl, DTBMS: di-t-butylmethylsilyl, IPDMS: isopropyldimethylsilyl, TBDMS: t-butyldimethylsilyl and TDS: thexyldimethylsilyl, preferably t-butyldimethylsilyl), a trialkylarylsilyl group (such as DPMS: diphenylmethylsilyl, TBDPS: t-butyldiphenylsilyl, TBMPS: t-butyldimethoxyphenylsilyl and TPS: triphenylsilyl), an alkylsulfonyl group (such as Ms: methane sulfonyl and ethane sulfonyl), and an aryl sulfonyl group (such as benzene sulfonyl, Ts: p-toluene sulfonyl, p-chlorobenzene sulfonyl, MBS: p-methoxybenzene sulfonyl, m-nitrobenzene sulfonyl, iMds: 2,6-dimethoxy-4-methylbenzene sulfonyl, Mds: 2,6-dimethyl-4-methoxybenzene sulfonyl, Mtb: 2,4,6-trimethoxybenzene sulfonyl, Mte: 2,3,5,6-tetramethyl-4-methoxybenzene sulfonyl, Mtr: 2,3,6-trimethyl-4-methoxybenzene sulfonyl, Mts: 2,4,6-trimethylbenzene sulfonyl and Pme: pentamethylbenzene sulfonyl), preferably a hydrogen atom, methyl, ethyl, n-propyl, i-propyl, cyclopropyl, methoxy,

ethoxy, n-propoxy, i-propoxy, methoxymethyl, ethoxymethyl, carboxyl and methoxycarbonyl, preferably a hydrogen atom, methyl, methoxymethyl, carboxyl and methoxycarbonyl.

Y is bonded on the carbon atom at the 2-, 3-, 4-, 5-, 6- or 7-position of the indole ring, more preferably on the carbon atom at the 2- or 5-position.

In the definition of Y:

R^6 is a hydrogen atom, a C_1-C_7 alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl) or a C_3-C_7 cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopropyl). It is preferably a hydrogen atom or methyl, more preferably a hydrogen atom.

R^7 is a hydrogen atom, a C_1-C_7 alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl) or a C_3-C_7 cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopropyl), or forms a bond together with R^4. It is preferably a hydrogen atom, or forms a bond together with R^4.

X^1 is S or O, preferably S.

X^2 is S, O or NH, preferably O or S, more preferably

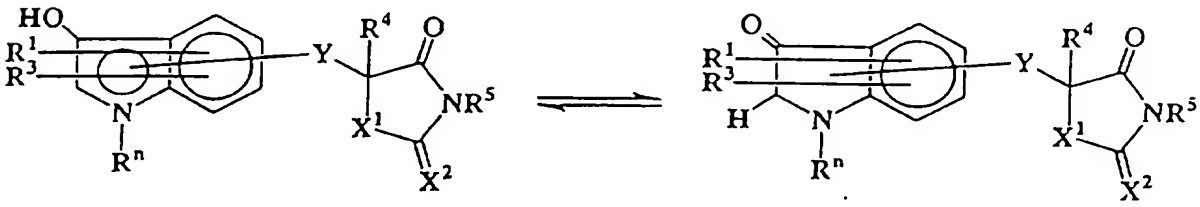
O.

In the present specification, "n" means normal, "i" means iso, "s" means secondary, "t" means tertiary, "c" means cyclo, "Me" means methyl, "Et" means ethyl, "Pr" means propyl, "Bu" means butyl, "Pen" means pentyl, "Hex" means hexyl, "Ph" means phenyl, and "Hal" means halogen.

Among these compounds, there is a compound having an asymmetric carbon atom at the 5-position of thiazolidine ring. The compound having the above formula (I) includes all of these optical isomers and their mixtures.

When R^2 is a substituent at the 3-positon of an indole ring and is a hydroxyl group, the following tautomer may form between the 2-position and the 3-position of an indole ring. The present invention includes all of these tautomers.

Indole type thiazolidines of the following formula and their salts.

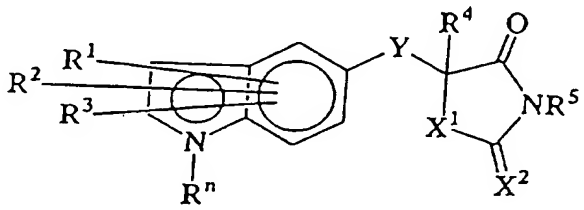


(wherein X^1, X^2, Y, R^4, R^5 and R^n are substituents as defined in the formula (I); R^1 is a substituent at the 2-, 4-, 5-, 6- or 7-position of an indole ring and is a substituent as defined in the formula (I); R^2 is a hydroxyl group at the 3-position of an indole ring; and

R^3 is a substituent at the 2-, 4-, 5-, 6- or 7-position of an indole ring and is a substituent as defined in the formula (I)).

The following compounds (1) to (24) may be mentioned as preferred examples of the compound of the formula (I) of the present invention.

(1) The indole type thiazolidine compound and its salt of the present invention, wherein the compound of the formula (I) is represented by the following formula (Ia):



(Ia)

wherein R^1 is a substituent at the 2-, 3-, 4-, 6- or 7-position of an indole ring, and is a hydrogen atom, a C_1-C_{10} alkyl group, a C_2-C_{10} alkenyl group, a C_2-C_{10} alkynyl group, a C_1-C_{10} alkoxy group, a C_2-C_{10} alkenyloxy group, a C_1-C_{10} alkylthio group, a C_1-C_{10} monoalkylamino group or a di-C_1-C_{10} alkylamino group (each of said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyloxy, C_1-C_{10} alkylthio, C_1-C_{10} monoalkylamino and di-C_1-C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1-C_7 alkyl group), or

$-W_k-W_\ell-Z$ (among groups of Z as defined for the formula (I), said C_3-C_{10} cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,

cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl, said C_3-C_7 cycloalkenyl group is cyclohexenyl, cyclopentadienyl, 2-bicylo[2.2.1]heptenyl or 2,5-bicyclo[2.2.1]heptadienyl, said C_6-C_{14} aromatic group is phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C_1-C_{12} heterocyclic aromatic group is furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl, oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl, pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl, pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl, benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl, benzothiazolyl, benzopyrazolyl, benzimidazolyl, benzotriazolyl, benzopyranyl, indolizinyl, purinyl, phthalazinyl, oxophthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxolyl, benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl, benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, or thianthrenyl, and said C_1-C_6 heterocycloaliphatic group is piperidyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, or

tetrahydrofuranyl, (each of said C_3-C_{10} cycloalkyl, C_3-C_7 cycloalkenyl, C_6-C_{14} aromatic, C_1-C_{12} heterocyclic aromatic and C_1-C_6 heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a

C_1-C_3 alkyl group),

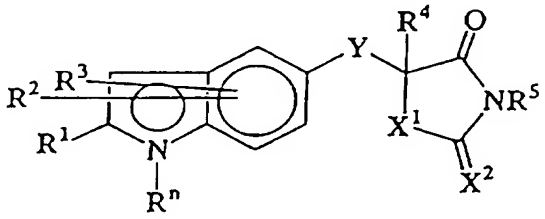
W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and

each of k and ℓ is 0 or 1),

-V-W-Z (V, W and Z are as defined above), or

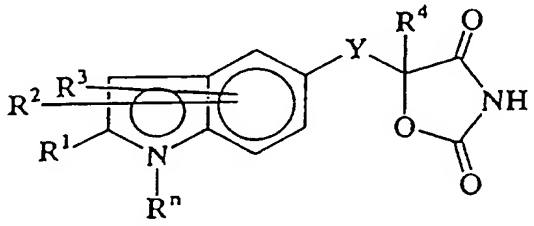
-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different).

(2) The indole type thiazolidine compound and its salt according to the above-mentioned (1), wherein the compound of the formula (Ia) is represented by the formula (Ib):



(Ib)

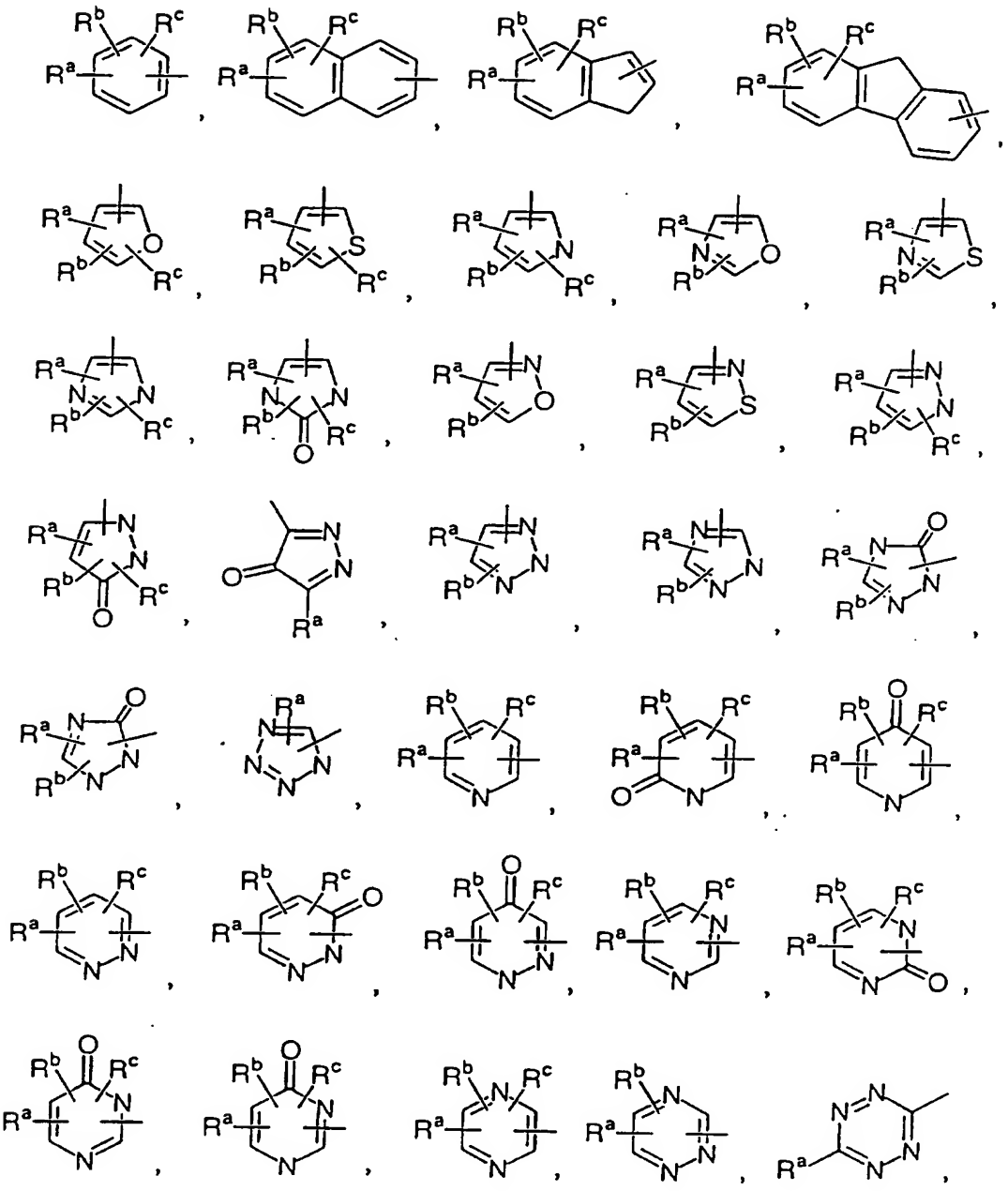
(3) The indole type thiazolidine compound and its salt according to the above-mentioned (2), wherein the compound of the formula (Ib) is represented by the following formula (Ic):

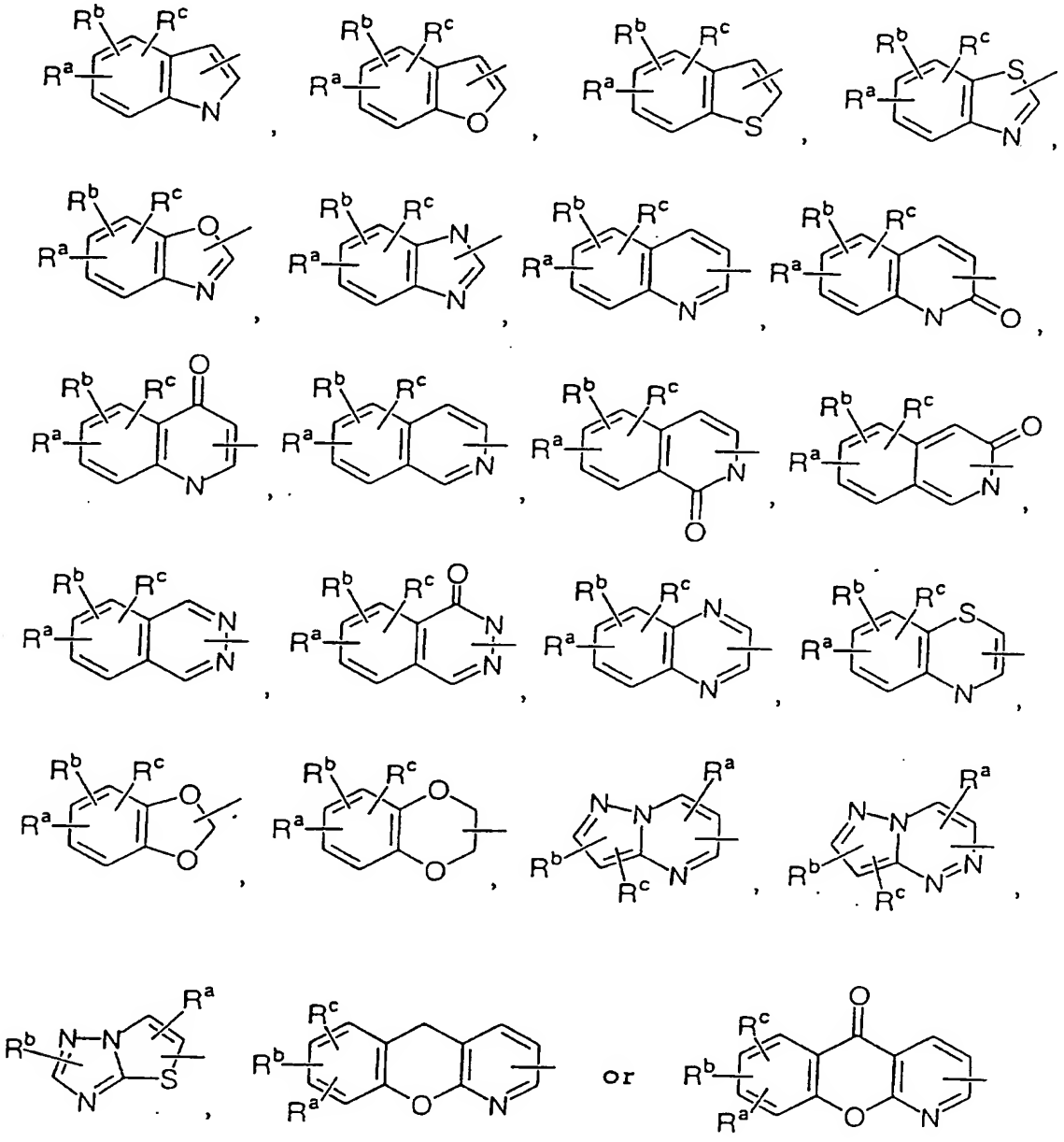


(Ic)

wherein R^1 is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen

atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, when two W's are present, such W's may be the same or different, and Z is





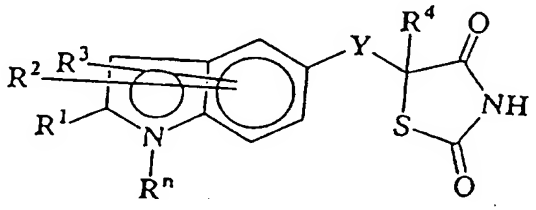
wherein each of R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a

C_3-C_6 cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and

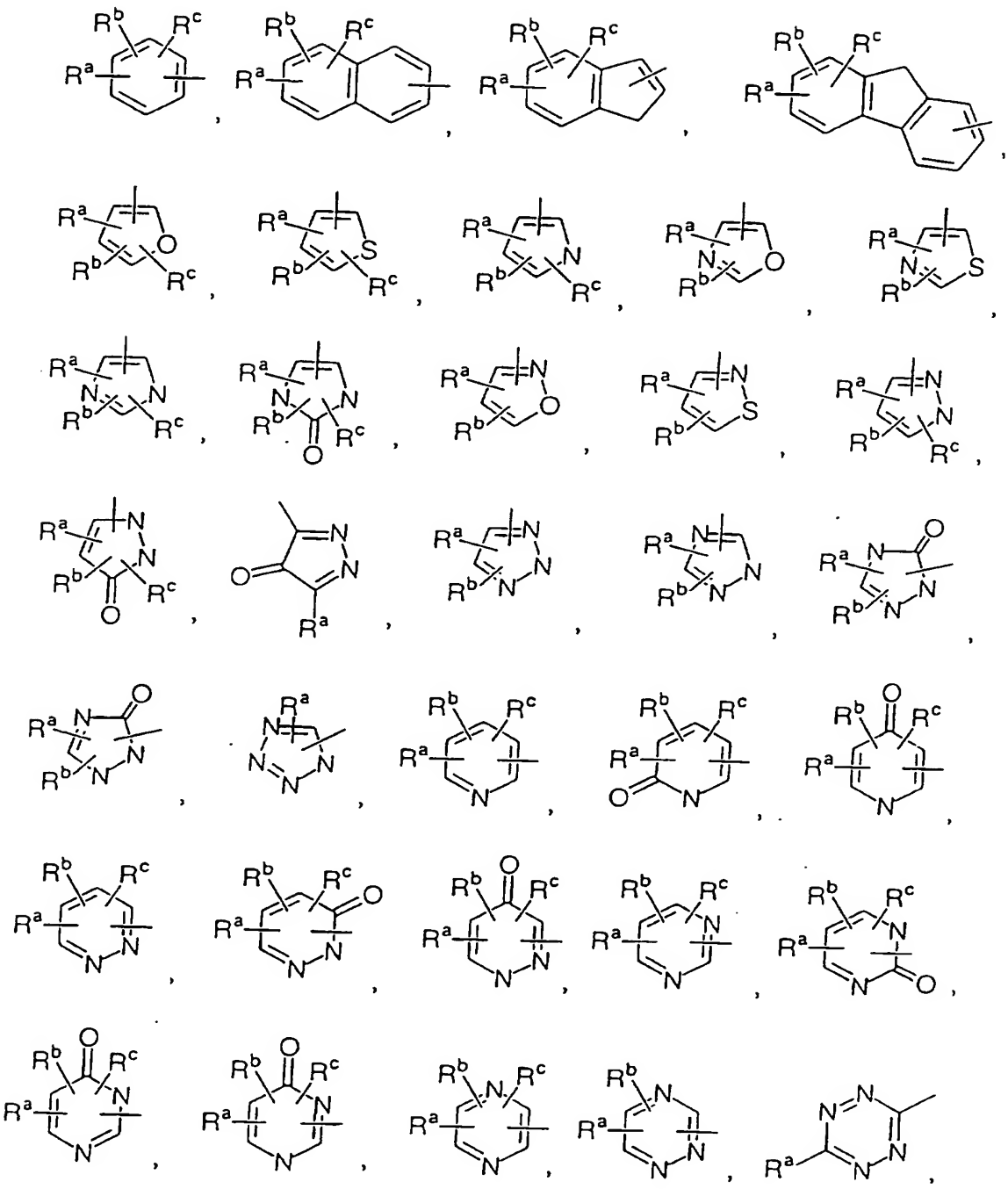
R^5 is a hydrogen atom.

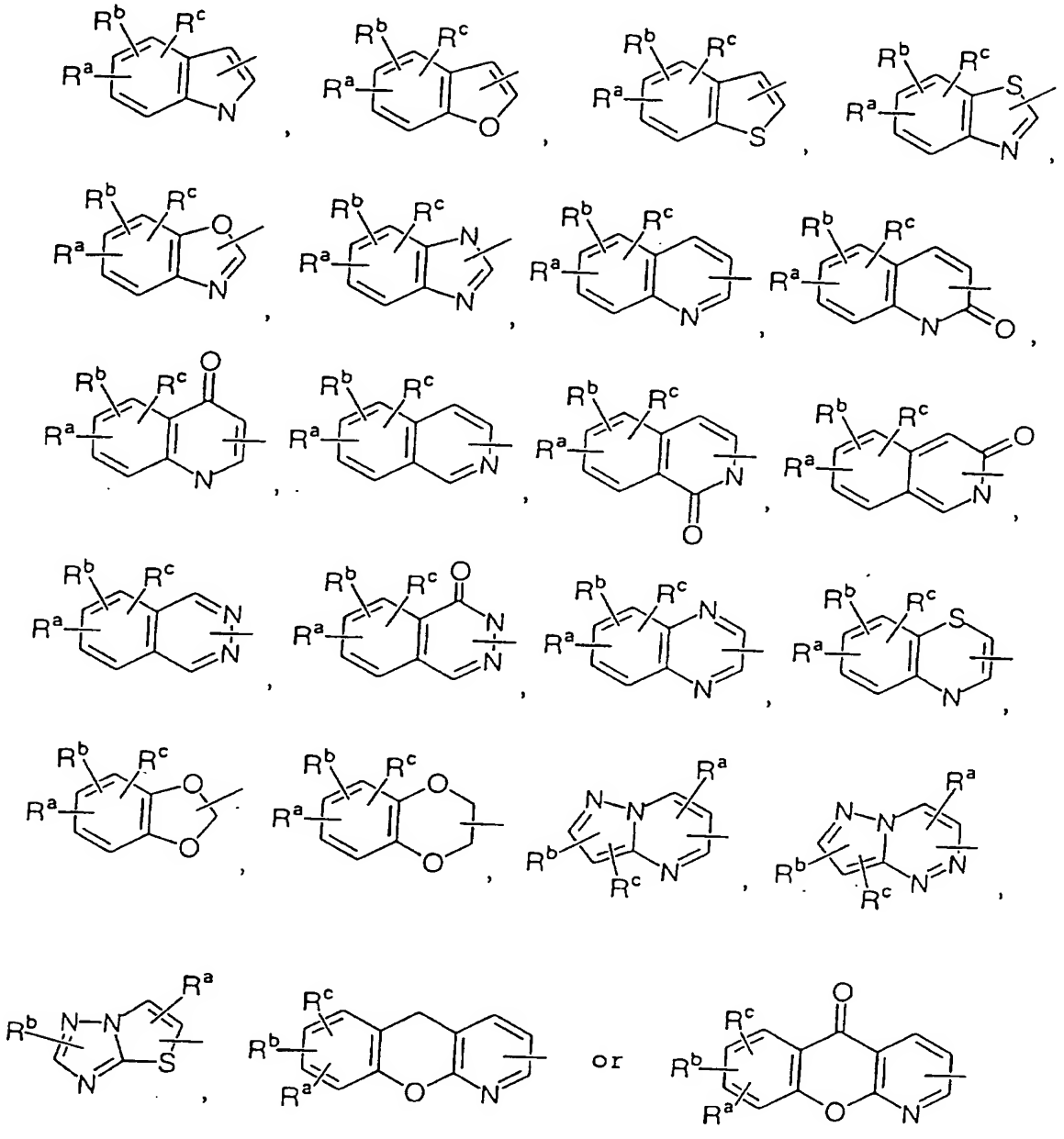
(4) The indole type thiazolidine compound and its salt according to the above-mentioned (2), wherein the compound of the formula (Ib) is represented by the following formula (Id):



(Id)

wherein R^1 is a substituent at the 2-positioin of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, when two W's are present, such W's may be the same or different, and Z is





wherein each of R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

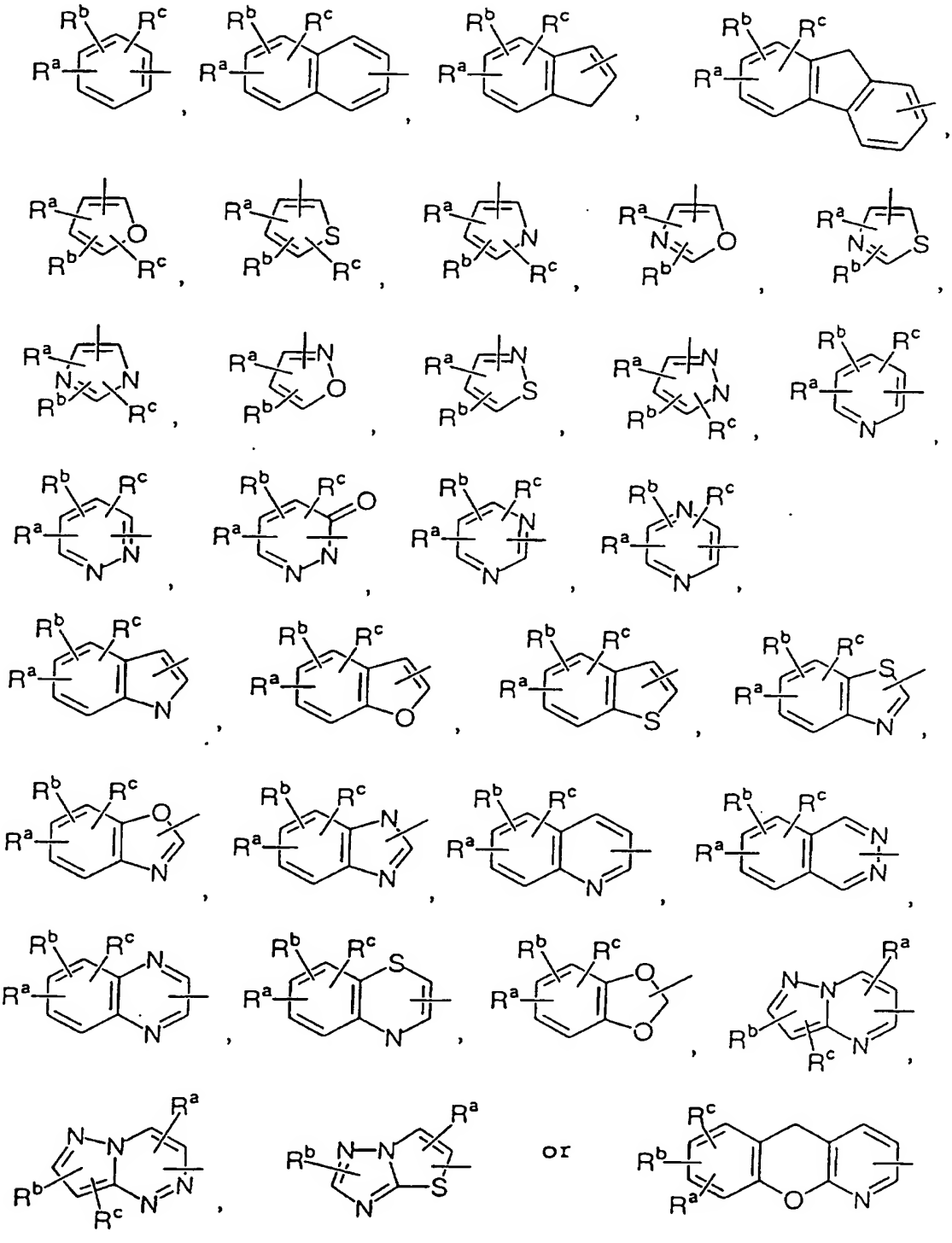
R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a

C_3-C_6 cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and

R^5 is a hydrogen atom.

(5) The indole type thiazolidine compound and its salt according to the above-mentioned (4), wherein: Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4);

R^1 is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups (provided that the first carbon atom bonded to N is not substituted with a hydroxyl group, and also provided that the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group) when two W's are present, such W's may be the same or different, and Z is



wherein each R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^4 is a hydrogen atom or a methyl group, or forms a bond together with R^7; and

R^n is a substituent at the 1-position of an indole

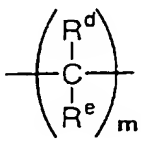
ring, and is a hydrogen atom, a C_1-C_3 alkyl group, a cyclopropyl group, a C_1-C_2 alkoxymethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C_1-C_3 alkoxy group, and a trialkylsilyl group.

(6) The indole type thiazolidine compound and its salt according to the above-mentioned (5), wherein:

R^1 is -W-Z, wherein W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 2 of hydroxyl, oxo and C_1-C_7 alkyl groups.

(7) The indole type thiazolidine compound and its salt according to the above-mentioned (6), wherein:

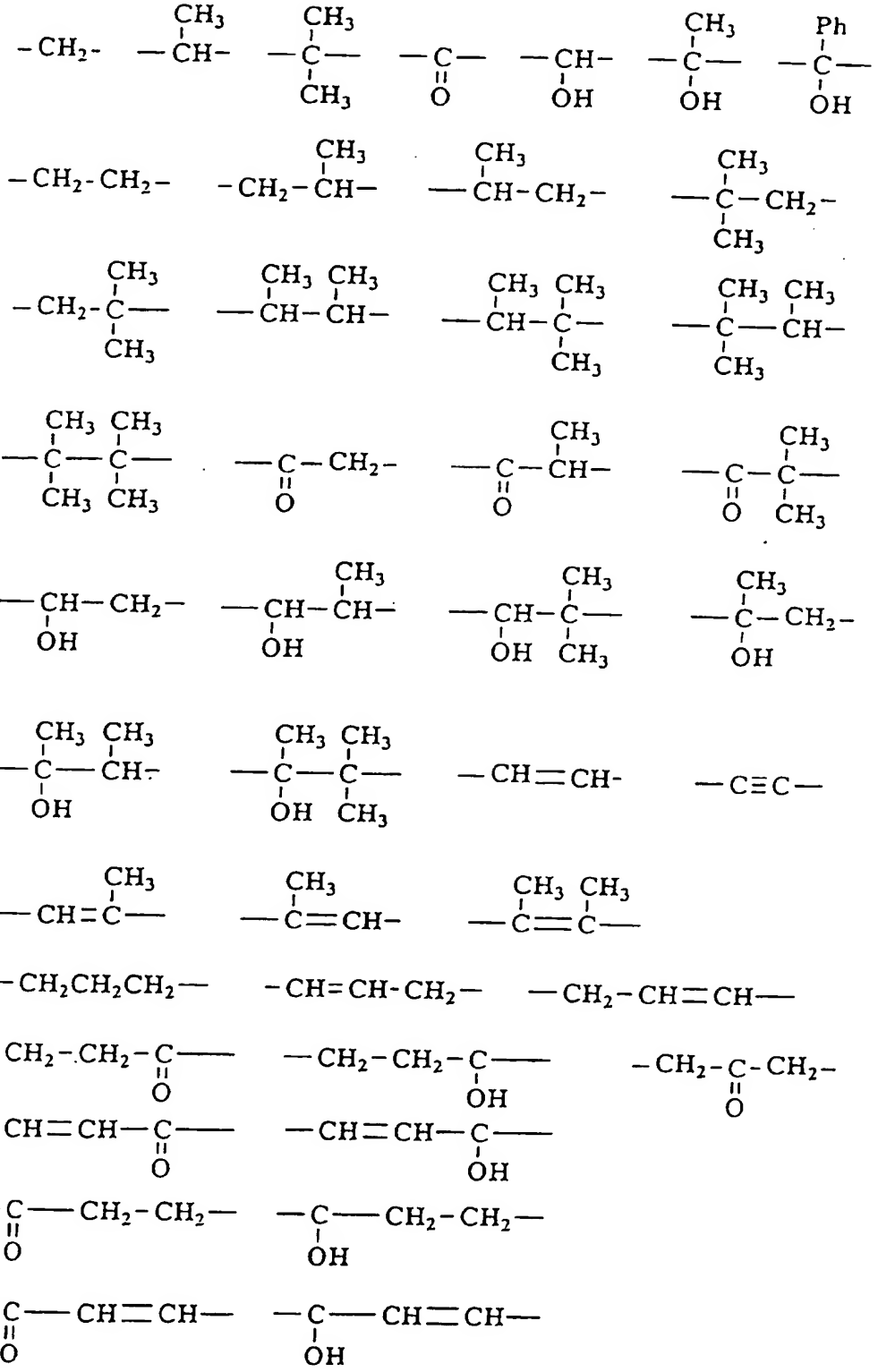
R^1 is -W-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond.

(8) The indole type thiazolidine compound and its salt according to the above-mentioned (7), wherein:

R^1 is -W-Z, wherein W is

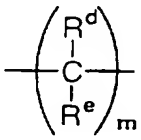


(9) The indole type thiazolidine compound and its salt according to the above-mentioned (5), wherein:

R^1 is -V-Z, wherein V is S, SO or SO_2.

(10) The indole type thiazolidine compound and its salt according to the above-mentioned (5), wherein:

R^1 is -W-V-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to N are not hydroxyl groups and also provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group),

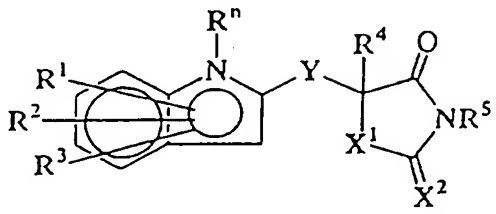
V is NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group).

(11) The indole type thiazolidine compound and its salt according to the above-mentioned (10), wherein:

R^1 is -W-V-Z, wherein -W-V- is $-CO-NR^8-$ (R^8 is a hydrogen atom or a C_1-C_3 alkyl group).

(12) The indole type thiazolidine compound and its salt of the present invention, wherein the compound of the formula (I) is represented by the following formula

(Ie):



(Ie)

wherein R^1 is a substituent at the 3-, 4-, 5-, 6- or 7-position of an indole ring, and is a C_1-C_{10} alkyl group, a C_2-C_{10} alkenyl group, a C_2-C_{10} alkynyl group, a C_1-C_{10} alkoxy group, a C_2-C_{10} alkenyloxy group, a C_1-C_{10} alkylthio group, a C_1-C_{10} monoalkylamino group or a di-C_1-C_{10} alkylamino group (each of said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyloxy, C_1-C_{10} alkylthio, C_1-C_{10} monoalkylamino and di-C_1-C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1-C_7 alkyl group), or

$-W_k-V_\ell-Z$ (among groups of Z as defined for the formula (I), said C_3-C_{10} cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl, said C_3-C_7 cycloalkenyl group is cyclohexenyl, cyclopentadienyl, 2-bicylo[2.2.1]heptenyl or 2,5-bicyclo[2.2.1]heptadienyl, said C_6-C_{14} aromatic group is phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C_1-C_{12} heterocyclic aromatic group is furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl,

oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl, pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl, pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl, benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl, benzothiazolyl, benzopyrazolyl, benzimidazolyl, benzotriazolyl, benzopyranyl, indolizinyl, purinyl, phthalazinyl, oxophthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxolyl, benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl, benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, or thianthrenyl, and said C_1-C_6 heterocycloaliphatic group is piperidyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, or tetrahydrofuranyl, (each of said C_3-C_{10} cycloalkyl, C_3-C_7 cycloalkenyl, C_6-C_{14} aromatic, C_1-C_{12} heterocyclic aromatic and C_1-C_6 heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a

trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group),

W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and

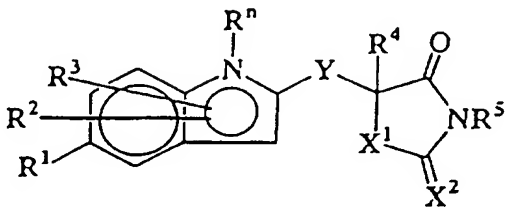
each of k and ℓ is 0 or 1),

-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different).

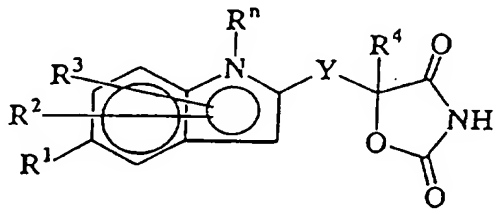
(13) The indole type thiazolidine compound and its

salt according to the above-mentioned (12), wherein the compound of the formula (Ie) is represented by the formula (If):



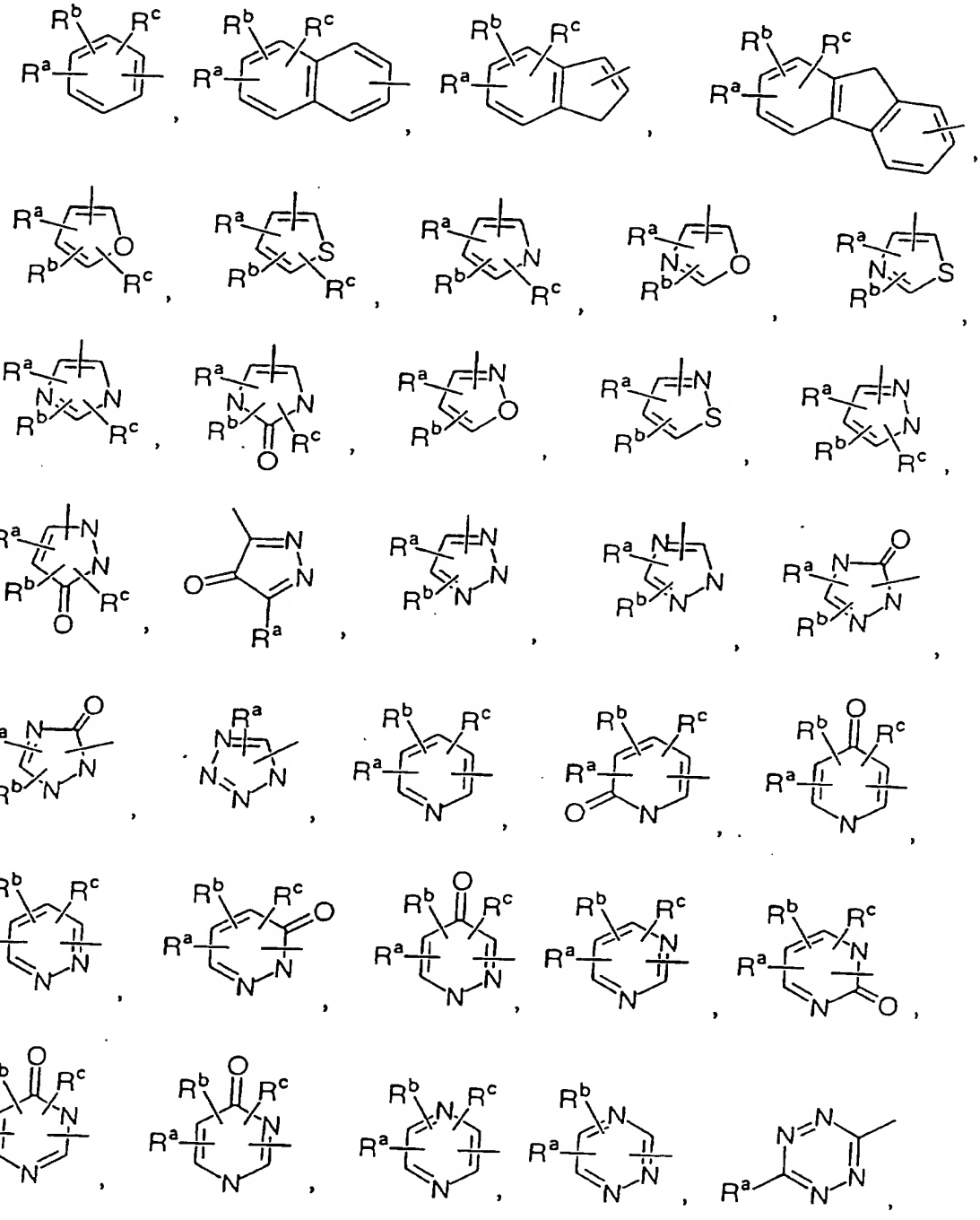
(If)

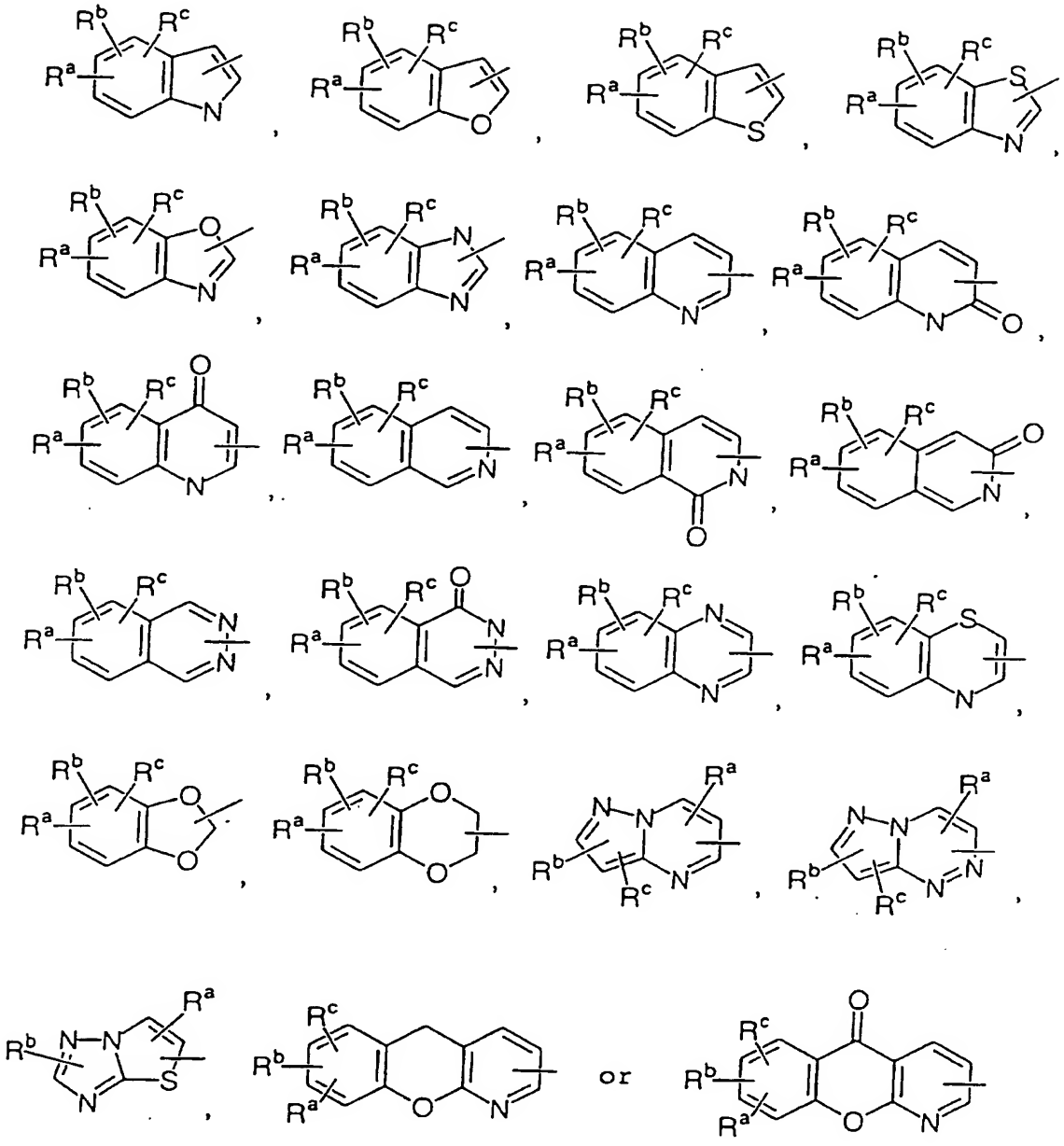
(14) The indole type thiazolidine compound and its salt according to the above-mentioned (13), wherein the compound of the formula (If) is represented by the following formula (Ig):



(Ig)

wherein R^1 is a substituent at the 5-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, when two W's are present, such W's may be the same or different, and Z is





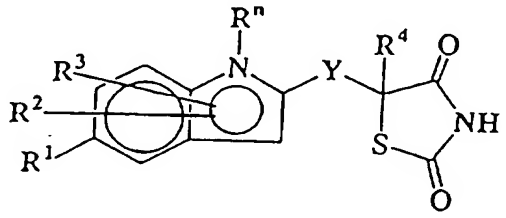
wherein each of R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a

C_3-C_6 cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and

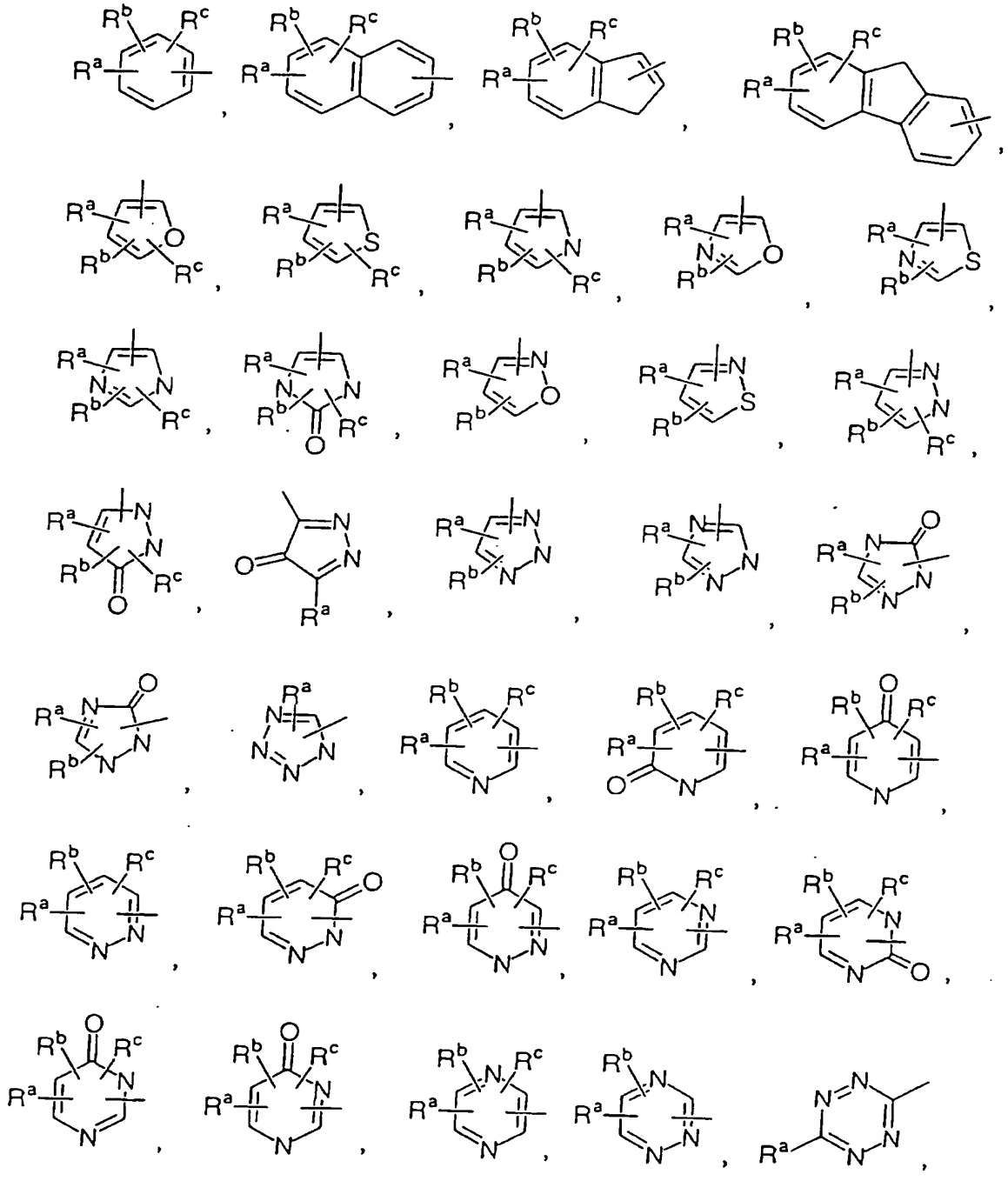
R^5 is a hydrogen atom.

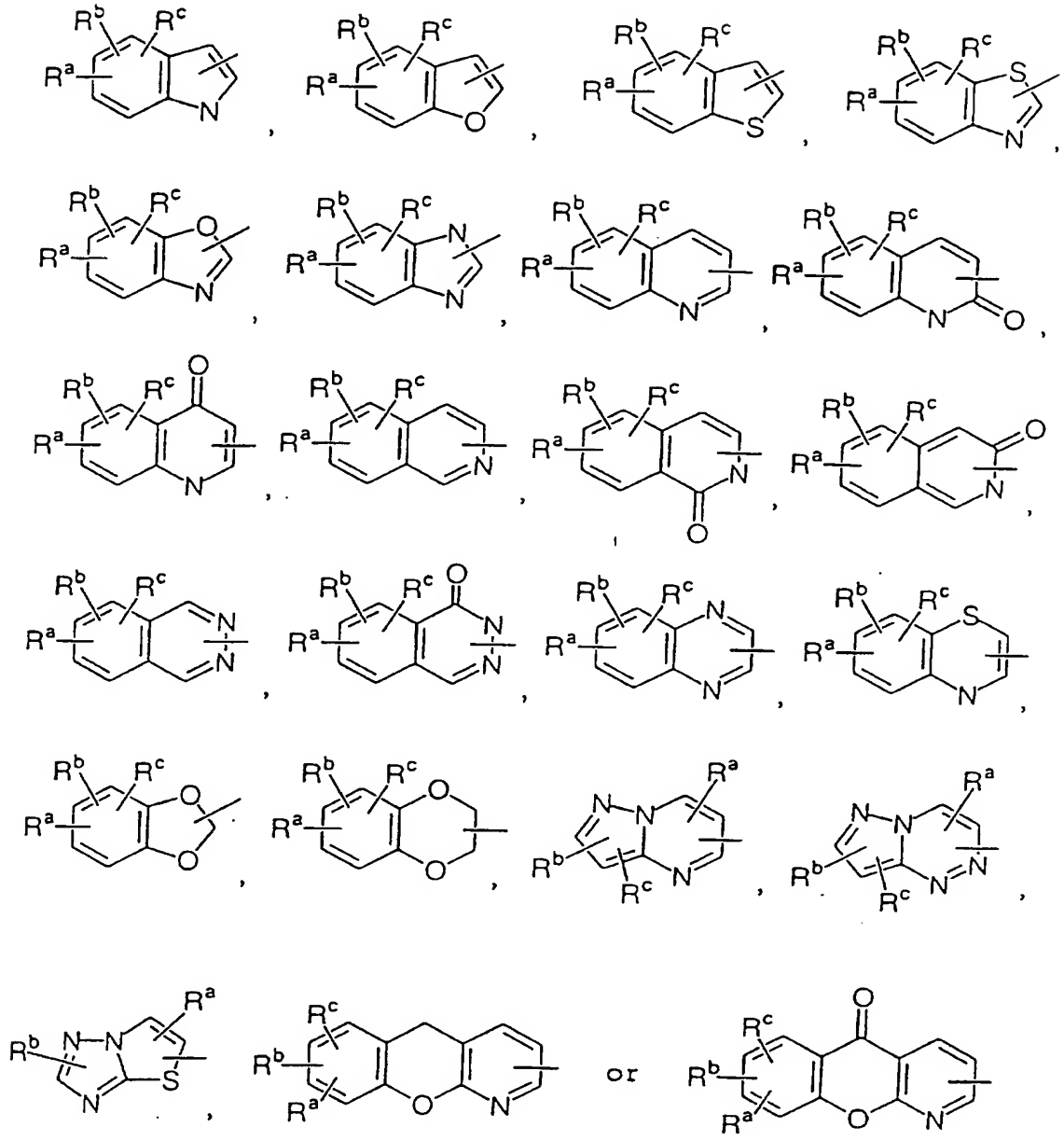
(15) The indole type thiazolidine compound and its salt according to the above-mentioned (13), wherein the compound of the formula (If) is represented by the following formula (Ih):



(Ih)

wherein R^1 is -V-W-Z, -W-Z, -V-W-V-W-Z, -W-V-W-Z, -V-W-V-Z or -W-V-Z (V is O, S or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, when two V's or W's are present, such V's or W's may be the same or different, and Z is





wherein each of R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

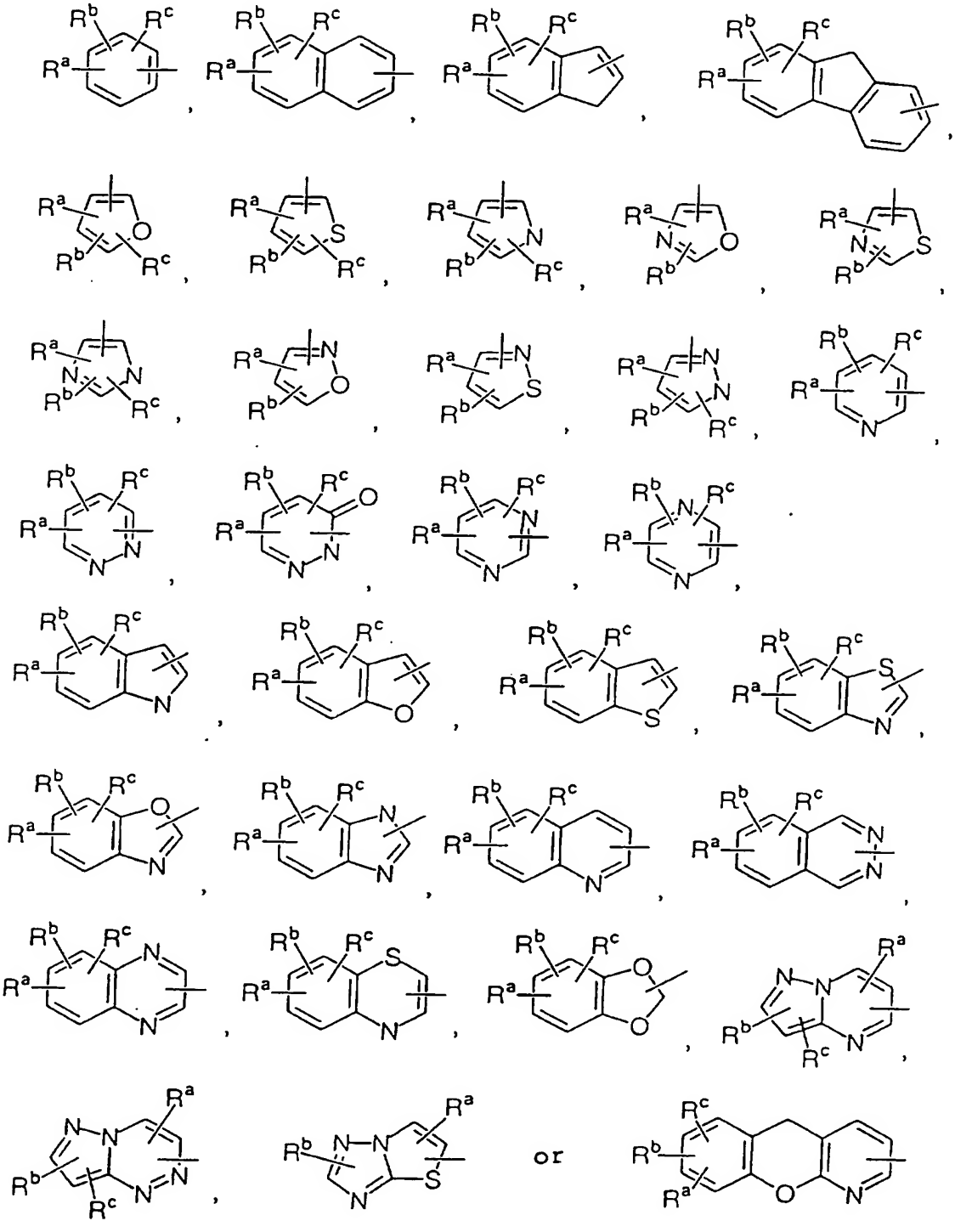
R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a

C_3-C_6 cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and

R^5 is a hydrogen atom.

(16) The indole type thiazolidine compound and its salt according to the above-mentioned (15), wherein: Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4);

R^1 is a substituent at the 5-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups (provided that the first carbon atom bonded to N is not substituted with a hydroxyl group, and also provided that the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group), when two W's are present, such W's may be the same or different, and Z is



wherein each R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^4 is a hydrogen atom or a methyl group, or forms a bond together with R^7; and

R^n is a substituent at the 1-position of an indole

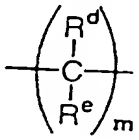
ring, and is a hydrogen atom, a C_1-C_3 alkyl group, a cyclopropyl group, a C_1-C_2 alkoxymethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C_1-C_3 alkoxy group, and a trialkylsilyl group.

(17) The indole type thiazolidine compound and its salt according to the above-mentioned (16), wherein:

R^1 is -W-Z, wherein W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 2 of hydroxyl, oxo and C_1-C_7 alkyl groups.

(18) The indole type thiazolidine compound and its salt according to the above-mentioned (17), wherein:

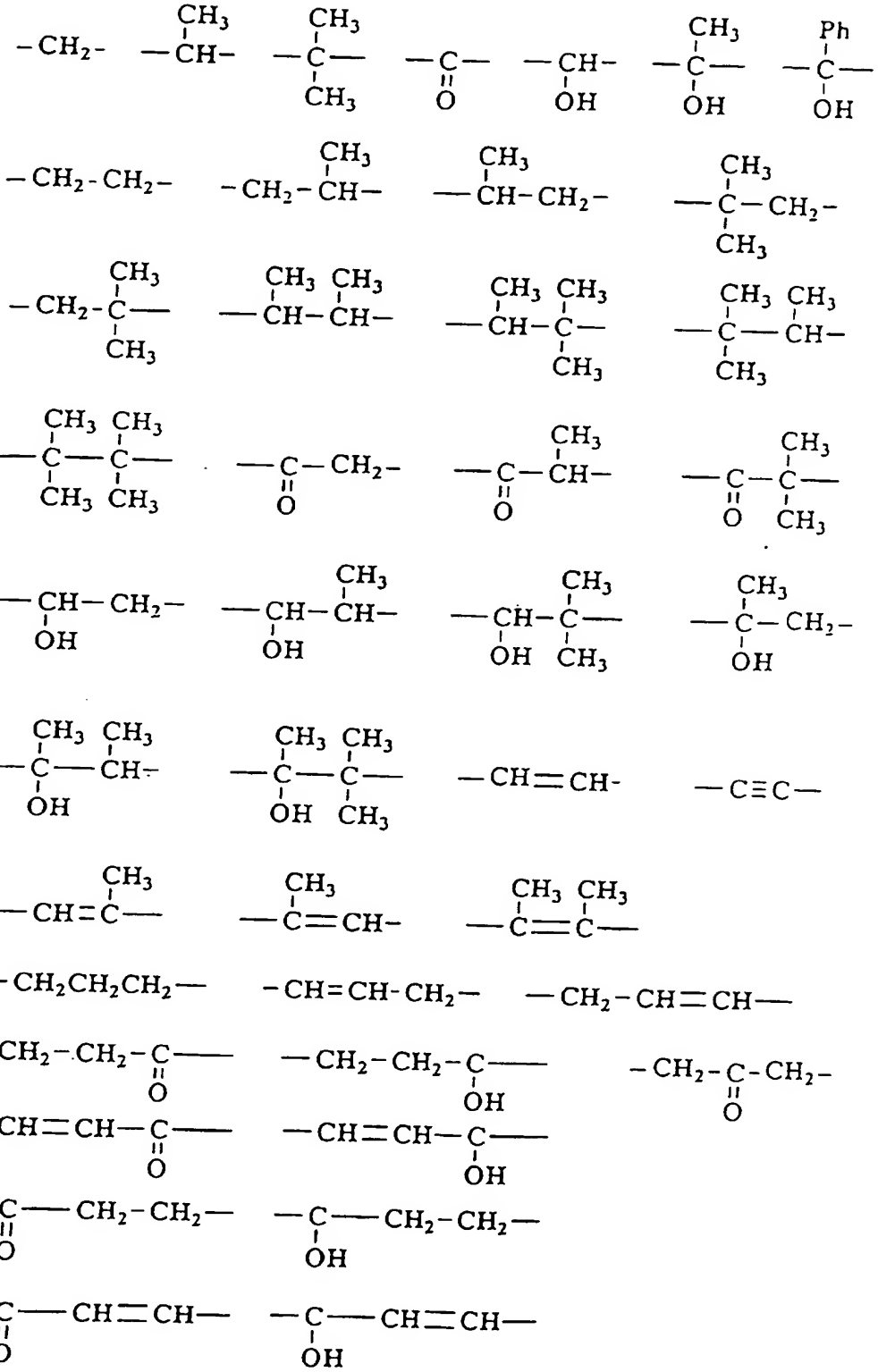
R^1 is -W-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond.

(19) The indole type thiazolidine compound and its salt according to the above-mentioned (18), wherein:

R^1 is -W-Z, wherein W is

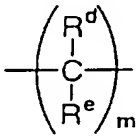


(20) The indole type thiazolidine compound and its salt according to the above-mentioned (16), wherein:

R^1 is -V-Z, wherein V is S, SO or SO_2.

(21) The indole type thiazolidine compound and its salt according to the above-mentioned (16), wherein:

R^1 is -W-V-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to N are not a hydroxyl group, and also provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group), and

V is NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group).

(22) The indole type thiazolidine compound and its salt according to the above-mentioned (21), wherein:

R^1 is -W-V-Z, wherein -W-V- is $-CO-NR^8-$ (R^8 is a hydrogen atom or a C_1-C_3 alkyl group).

(23) The indole type thiazolidine compound and its salt according to the above-mentioned (8), (9), (11), (19), (20) or (21), wherein:

Y is $-CH_2-$; and

R^4 is a hydrogen atom.

(24) The indole type thiazolidine compound and its salt according to the above-mentioned (8), (9), (11), (19), (20) or (21), wherein: Y is CHR^7 (R^7 forms a bond together with R^4), and R^4 forms a bond together with R^7.

The compound of the above formula (I) of the present invention has acidic hydrogen on a thiazolidine ring or on an oxazolidine ring. Further, when substituent Z is a heterocyclic aromatic group or a heterocyclic aliphatic group, it sometimes has a basic nitrogen. Such a compound may be converted to a pharmaceutically acceptable non-toxic salt with an appropriate base or acid, if desired. The compound of the formula (I) can be used for the purpose of the present invention either in the free form or in the form of a pharmaceutically acceptable salt. Examples of the basic salt include an alkali metal salt (lithium salt, sodium salt, potassium salt and the like), an alkali earth metal salt (calcium salt, magnesium salt and the like), an aluminum salt, an ammonium salt which may be unsubstituted or substituted with a methyl, ethyl or benzyl group, an organic amine salt (methylamine salt, ethylamine salt, dimethylamine salt, diethylamine salt, trimethylamine salt, triethylamine salt, cyclohexylamine salt, ethylenediamine salt, bicyclohexylamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, piperazine

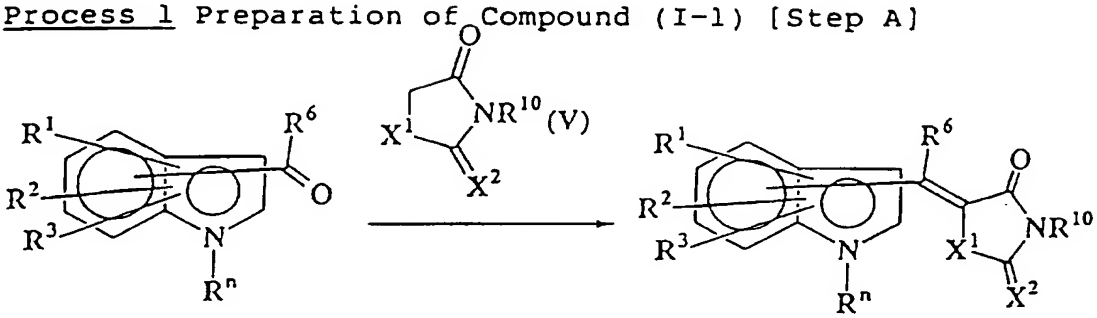
salt, dibenzylpiperidine salt, dehydroabietilamine salt, N,N'-bisdehydroabietilamine salt, benzathine(N,N'-dibenzylethylenediamine) salt, glucamine salt, meglumine(N-methylglucamine) salt, benetamine(N-benzylphenetylamine)salt, trometamine(2-amino-2-hydroxymethyl-1,3-propanediol)salt, choline salt, procaine salt), a basic amino acid salt (lysine salt, ornithine salt, arginine salt and the like), a pyridine salt, a collidine salt, a quinoline salt, and the like. Examples of an acid-addition salt include a mineral acid salt (hydrochloride, hydrobromide, sulfate, hydrogensulfate, nitrate, phosphate, hydrogenphosphate, dihydrogenphosphate and the like), an organic acid salt (formate, acetate, propionate, succinate, malonate, oxalate, maleate, fumarate, malate, citrate, tartrate, lactate, glutamate, asparate, picrate, carbonate and the like), a sulfonic acid salt (methanesulfonate, benzenesulfonate, toluenesulfonate and the like), and the like. Each of these salts can be prepared by a known method.

The compound having the formula (I), i.e. indole type thiazolidines, can be prepared by the following synthetic methods.

A reaction solvent used in the preparation is stable under the reaction conditions, and is preferably so inert as not to inhibit the reaction. Examples of the reaction solvent include water, alcohols (such as methanol,

ethanol, propanol, butanol and octanol), cellosolves (such as methoxyethanol and ethoxyethanol), aprotic polar organic solvents (such as dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetramethylurea, sulfolane and N,N-dimethylimidazolidinone), ethers (such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane), aliphatic hydrocarbons (such as pentane, n-hexane, c-hexane, octane, decaline and petroleum ether), aromatic hydrocarbons (such as benzene, chlorobenzene, nitrobenzene, toluene, xylene and tetralin), halogenated hydrocarbons (such as chloroform, dichloromethane and dichloroethane), ketones (such as acetone, methyl ethyl ketone and methyl butyl ketone), lower aliphatic acid esters (such as methyl acetate, ethyl acetate and methyl propionate), alkoxy alkanes (such as dimethoxyethane and diethoxyethane), acetonitrile, and the like. These solvents are optionally selected depending on the reactivity of the aimed reaction, and are respectively used alone or in a mixture. In some cases, there are used as an anhydrous solvent by using a dehydrating agent or a drying agent. The above-mentioned solvents are merely examples which can be used in the reaction of the present invention, and the present invention is not limited to these conditions.

Process 1 Preparation of Compound (I-1) [Step A]



(II) (I-1)
(R^4, R^7=bond)

(wherein R^1, R^2, R^3, R^6, R^n, X^1 and X^2 are as defined above, and R^{10} is a hydrogen atom or a protecting group of amide (such as Tr: trityl)).

A compound wherein R^4 and R^7 are bonded together in the formula (I), i.e. a compound of the formula (I-1), can be obtained by dehydration-condensation of a compound of the formula (II) and a compound of the formula (V). The compound of the formula (II) is a well known compound or can be synthesized by the method disclosed in Japanese Unexamined Patent Publication No. 271288/1991, Japanese Unexamined Patent Publication No. 277660/1988, Japanese Unexamined Patent Publication No. 71321/1975 or Japanese Examined patent Publication No. 34986/1974. The compound of the formula (V) is a well known compound or can be synthesized by the method disclosed in "J. Prakt. Chem." (vol. 2, p. 253, 1909), "J. Prakt. Chem." (vol. 3, p. 45, 1919), "Chem. Ber." (vol. 118, p. 774, 1985), and German Laid Open Patent Publication No. DE-3045059. The compound of the formula (V) wherein R^{10} is hydrogen, can be used in this reaction after displacing its acidic

hydrogen at the 3-position of thiazolidine or oxazolidine with an appropriate substituent (such as TR: trityl) by a well known method.

This reaction is conducted usually in an appropriate organic solvent in the presence of base or acid. Examples of such a solvent include alcohols, cellosolves, aprotic polar organic solvents, ethers, aromatic hydrocarbons, halogenated hydrocarbons, alkoxyalkanes and acetonitrile.

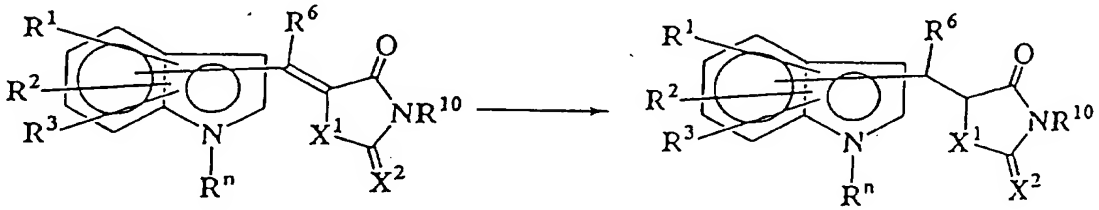
Examples of the base and the acid include organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine), Acid Capture H: 3,4-dihydro-2H-pyrid[1,2-a]pyrimidin-2-one, Acid Capture 9M: 9-methyl-3,4-dihydro-2H-pyrid[1,2-a]pyrimidin-2-one, and the like, or metal alkoxides (such as sodium methoxide, sodium ethoxide, lithium isopropoxide and potassium t-butoxide), inorganic alkali metal salts (such as potassium carbonate, sodium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydride, potassium hydride, calcium hydride, sodium acetate and potassium acetate), organic acids (such as acetic acid, trichloroacetic acid and trifluoroacetic acid), inorganic acids (such as phosphoric acid), and the like. These materials are selected appropriately depending on the reactivity of the

aimed reaction.

This reaction can be accelerated by removing water formed during the reaction out of the system by using an appropriate dehydrating agent such as molecular sieves and anhydrous sodium sulfate or by azeotropic distillation using Dean-Stark tube.

This reaction is conducted usually at a temperature ranging from 0°C to a boiling point of a solvent used, preferably from 20°C to 120°C, for from 0.5 to 30 hours.

Process 2 Preparation of Compound (I-2) [Step B]



(I-1)
(R^4, R^7=bond)

(I-2)
(R^4=H, R^7=H)

(wherein R^1, R^2, R^3, R^6, R^{10}, R^n, X^1 and X^2 are as defined above).

A compound of the formula (I-I) (R^4 and R^7 together form a bond) obtained by the above method can be converted into a compound of the formula (I-2) (R^4 and R^7=H) in accordance with an appropriate reduction method, for example by catalytically hydrogenating in the presence of an appropriate catalyst, or by using an appropriate metal-hydrogen complex compound, or by reducing a double bond connecting an indole ring with a

thiazolidine or oxazolidine ring in a lower alcohol such as methanol by magnesium or sodium amalgam.

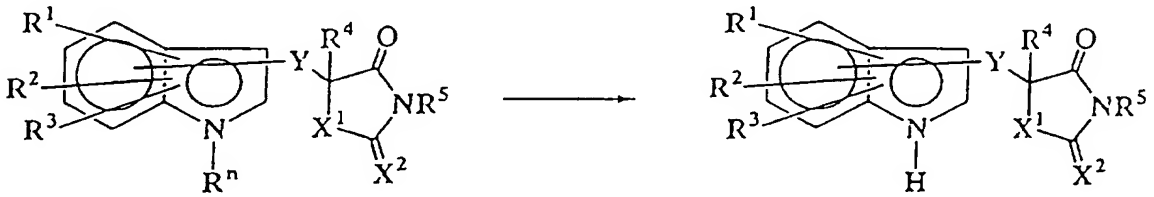
The reduction reaction by catalytic hydrogenation is conducted usually in a solvent such as water, alcohols, cellosolves, aprotic polar organic solvents, ethers, alkoxyalkanes, lower aliphatic acid esters or lower aliphatic acids, preferably water, methanol, ethanol, methoxyethanol, dimethylformamide, dimethylacetamide, tetrahydrofuran, dioxane, dimethoxyethane, ethylacetate or acetic acid. The solvent may be used alone or in a mixture. Examples of the catalyst used in this reaction include Raney nickel, palladium black, palladium carbon, ruthenium carbon, platinum oxide and the like. This reaction proceeds usually at normal temperature and a atmospheric pressure but it is preferable for accelerating the procedure of the reaction to optionally employ an elevated temperature and a higher pressure.

In the case of the reduction reaction using a metal-hydrogen complex compound, a reaction is conducted in water or an appropriate organic solvent at a temperature of from 0°C to 150°C, preferably from 0°C to 30°C, and examples of the metal-hydrogen complex compound include sodium borohydride, potassium borohydride, lithium borohydride, sodium cyanoborohydride, potassium tri-s-butylborohydride, potassium triethylborohydride, lithium triethylborohydride, sodium triethylborohydride, tetramethylammonium borohydride, tetra-n-butylammonium

borohydride, tetra-n-butylammonium cyanoborohydride, sodium triacetoxyborohydride, tetra-n-butylammonium triacetoxyborohydride, lithium thexylborohydride, potassium triphenylborohydride, sodium trimethoxyborohydride, rhodium borohydride, tetraethylammonium borohydride, methyltrioctylammonium boronydride, calcium borohydride bis(tetrahydrofuran), lithium dimethylborohydride, zinc borohydride and the like. Also, in this reduction, an undesired side reaction can be inhibited by adding a Co reagent such as $CoCl_2$, $CoCl_3$ and $Co(OAc)_2$ in the presence of a ligand such as dimethyl glyoxime, 2,2'-dipyridyl and 1,10-phenanthroline (see WO 93/13095).

In the case of the reduction using an amalgam, the reaction is conducted in a solvent such as alcohols, preferably ethanol or ethanol at a temperature of from -20°C to a boiling point of a solvent used, preferably from 0°C to 50°C. Also, the reduction method by magnesium/methanol can be employed, as described in "J. Org. Chem.", vol. 40, P 127 (1975).

Process 3 Preparation of Compound (I) (Displacement of substituent R^n) [Step C]



(I)
($R^n \neq H$)

(I)
($R^n = H$)

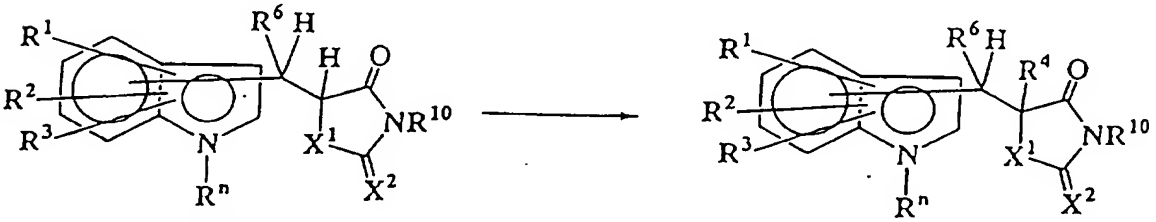
(wherein R^1, R^2, R^3, R^4, R^5, X^1, X^2 and Y are as defined above, R^n is a substituent (other than a hydrogen atom) at the 1-position of an indole ring).

Among the compounds of the formula (I), the R^n substituent other than a hydrogen atom at the 1-position of an indole ring can be converted to a hydrogen atom by a well known appropriate method. The following reaction conditions can be employed depending on the type of the substituent R^n.

The displacement of the R^n substituent can be conducted by heat-refluxing for 1 to 12 hours in a mixture solution of sodium hydroxide aqueous solution/ethanol when R^n is a benzenesulfonyl group, a p-toluenesulfonyl group or a p-methoxybenzenesulfonyl group; by catalytically reducing in the presence of palladium carbon, lithium aluminum hydride or Raney nickel in methanol, ethyl acetate or tetrahydrofuran when R^n is a methoxy group, a methoxymethyloxy group, a methoxyethyloxy group or a benzyloxymethyloxy group; by stirring at room temperature in trifluoroacetic acid, a mixture solution of sodium hydroxide/methanol or a mixture solution of hydrochloric acid aqueous solution/methanol when R^n is a tertiary butylamino carbonyl group or a tertiary butoxy carbonyl group; by using tetra-n-butylammonium fluoride or cesium fluoride in tetrahydrofuran at room temperature when R^n is a trimethylsilyl group, a tertiary butyldimethylsilyl

group, a tertiary butyldiphenylsilyl group or a triisopropylsilyl group; by stirring at room temperature in a mixture solution of sodium hydroxide aqueous solution/ethanol when R^n is an acetyl group or a trifluoroacetyl group; by using tetrabutylammonium fluoride or a cesium fluoride at room temperature in tetrahydrofuran when R^n is a trimethylsilylethyloxymethyl group; by using lithium bromide and boron trifluoride/ether complex and acetic anhydride when R^n is a methoxymethyl group; by using sodium methoxide or sodium borohydride in methanol at room temperature when R^n is a dimethylaminomethyl group; or by heating at 80°C to 200°C and decarboxylating when R^n is a carboxyl group, thus converting the substituent at the 1-position to a hydrogen atom.

Process 4 Displacement of R^4 substituent of Compound (I-2) [Step D]



(I-2)
(R^4=H, R^7=H)

(I-2)
(R^4≠H, R^7=H)

(wherein R^1, R^2, R^3, R^4, R^6, R^{10}, X^1 and X^2 are as defined above).

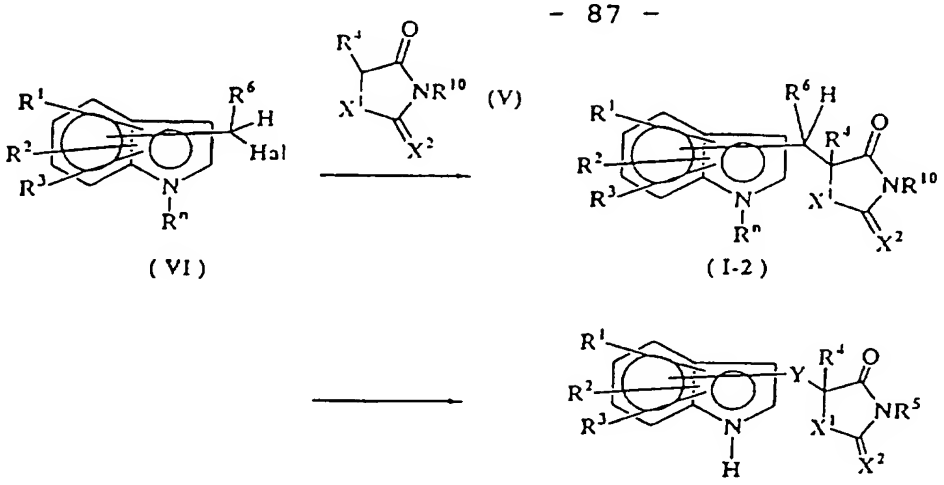
A compound of the formula (I-2) (R^4, R^7=H) can be

converted into a compound of the formula (I-2) ($R^4 \neq H$, $R^7=H$) in accordance with a well known method by alkylating hydrogen at the 5-position of a thiazolidine or oxazolidine ring with an appropriate alkylating agent (such as alkylhalides including methyliodide and ethyliodide, alkylsulfates including dimethylsulfate and diethylsulfate, or aliphatic or aromatic sulfonic acid esters including methyltosylate and methylmesylate).

This reaction is conducted usually in the presence of a base in an appropriate organic solvent. Examples of the solvent used include aprotic polar organic solvents, ethers, and alkoxy alkanes, preferably tetrahydrofuran and dimethoxy ethane. Examples of the base include alkali metal amides (such as LDA: lithium diisopropyl amide and potassium amide), aliphatic or aromatic lithium compounds (such as n-butyl lithium, t-butyl lithium and phenyl lithium), and the like. These materials are selected optionally depending on the reactivity of the aimed reaction.

This reaction is conducted usually at a temperature in the range of from -20°C to 100°C, preferably from -10°C to 30°C for 0.1 to 10 hours.

Process 5 Preparation of Compound (I-2) [Step E] and Deprotection of R^{10}



(VI) (V) (I-2) (I)

(wherein R^1, R^2, R^3, R^4, R^6, R^{10}, R^n, X^1 and X^2 are as defined above, and R^{12} is an appropriate leaving group in nucleophilic displacement in the present reaction, examples of which include a halogen such as chloro, bromo and iodo, and an aromatic or aliphatic sulfonyloxy group such as p-toluenesulfonyloxy, benzenesulfonyloxy and methanesulfonyloxy).

A compound of the formula (I) other than the one wherein R^4 and R^7 together form a bond, i.e. a compound of the formula (I-2), can be obtained by reacting a compound of the formula (V) with an indole derivative of the formula (VI). The compound of the formula (V) used herein is a well known compound or can be synthesized by a method disclosed in "Ukr. Khim. Zh." (vol. 16, p. 545, 1950), "J. Med. Chem." (vol. 34, p. 1538, 1991), "J. Prakt. Chem." (vol. 2, 79, P. 259 (1909), "J. Prakt. Chem." (vol. 2, 99, P. 56 (1919) or Japanese Unexamined Patent Publication No. 216882/1984. The compound of the formula (V) wherein R^{10} is hydrogen, is used in this

reaction preferably after displacing its acidic hydrogen with an appropriate substituent (such as Tr: trityl) by a known method.

This reaction is conducted usually in an appropriate organic solvent in the presence of base. Examples of the solvent thus used include aprotic polar organic solvents (such as HMPA: hexamethylphosphoric triamide and DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidine), ethers (such as THF: tetrahydrofuran) and alkoxyalkanes, and the solvent may be used respectively alone or in a mixture. Examples of the base thus used include a strong base such as alkali metal amides (e.g. LDA: lithium diisopropyl amide, sodium amide and potassium amide) and aliphatic or aromatic lithium compounds (e.g. n-butyl lithium, t-butyl lithium and phenyl lithium). These materials are selected optionally depending on the reactivity of the aimed reaction.

The reaction using a compound of the formula (V) wherein R^4 and R^{10} are hydrogen, can be conducted in accordance with a method disclosed in "J. Labelled Compounds and Radiopharmaceuticals" (vol. XXVIII, No. 8, p. 911, 1990). In such a case, a compound of the formula (V) is reacted with n-butyl lithium usually in an inert gas atmosphere such as nitrogen and in a mixed solvent such as THF: HMPA=4:1 at a temperature of from -100°C to -10°C to form an anion, which is then reacted with an indole compound of the formula (VI) to obtain a compound

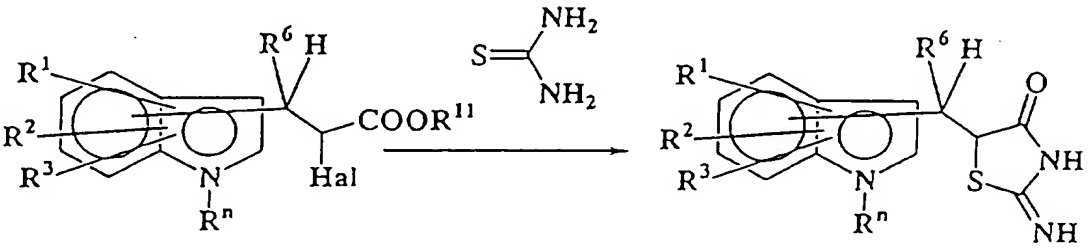
of the formula (I-2). The reaction of the anion and the indole compound (VI) is conducted usually at a temperature of from -50°C to 100°C, preferably from -10°C to room temperature. The reaction time may be varied depending on the materials used, but is usually from 0.5 to 1 hour for the formation of an anion and from 0.5 to 5 hours for the reaction with an indole compound.

Also, this reaction can be conducted in accordance with a method disclosed in "J. Amer. Chem. Soc." (vol. 87, p. 4588, 1965) or "J. Med. Chem." (vol. 34, p. 1538, 1991). In such a case, a compound of the formula (V) is reacted with magnesium methylcarbonate in an inert gas atmosphere such as nitrogen and in an aprotic polar organic solvent such as dimethylformamide to form a chelate compound, and the chelate compound thus formed is further reacted with an indole compound of the formula (VI) to obtain a compound of the formula (I-2). This reaction is conducted usually at a temperature ranging from 20°C to 150°C, preferably from 70°C to 100°C. The reaction time varies depending on the materials used, but the formation of the chelate compound takes from 0.5 to 2 hours and the reaction with the indole compound takes from 0.5 to 5 hours.

In some cases, an amide group at the 3-position of thiazolidine ring of the compound of the formula (I-2) thus obtained may be deprotected by a well-known method. When R^{10} is Tr (trityl), this method is conducted by

using an organic acid such as trifluoroacetic acid and trichloroacetic acid or an inorganic acid such as hydrochloric acid and sulfuric acid. This reaction is conducted in the absence of a solvent or in the presence of a solvent such as ethers including tetrahydrofuran and dioxane and halogenated solvents including chloroform and dichloromethane, at a temperature ranging from 0°C to 100°C, preferably from 10°C to 50°C, for 0.1 to 5 hours.

Process 6



(XII) (I-2c)

(R^4,R^7,R^{10}=H, X^1=S, X^2=NH)

(wherein R^1, R^2, R^3 and R^6 are as defined above, and R^{11} is C_1-C_4 alkyl such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, and Hal is a halogen atom such as a chlorine atom, a bromine atom and an iodide atom).

A compound of the formula (I) wherein R^4 and R^7 are H and X^1 is S and X^2 is NH, i.e. a compound of the formula (I-2c) (R^4, R^7=H, X^1=S, X^2=NH), can be obtained by reacting thiourea with a halocarboxylic acid ester of the formula (XII).

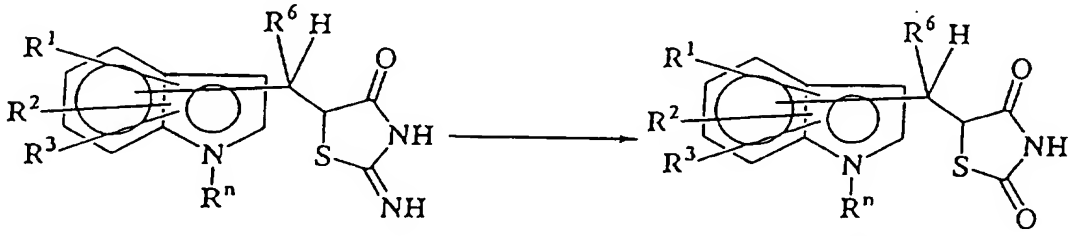
This reaction is conducted usually in an appropriate organic solvent in the presence of base or acid. Examples of the solvent used include alcohols,

cellosolves and aprotic polar organic solvents, preferably sulfolane.

This reaction is conducted at a temperature of from 0°C to a boiling point of a solvent used, preferably from 50°C to 150°C, for 0.5 to 10 hours.

As the reaction proceeds, a hydrogen halide is by produced, but the reaction can be accelerated by capturing the by-produced hydrogen halide with an appropriate base. Examples of the base used include organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine), inorganic alkali metal salts (such as sodium acetate and potassium acetate) and the like.

Process 7



(I-2c)
(X^1=S, X^2=NH)

(I-2d)
(X^1=S, X^2=O)

(wherein R^1, R^2, R^3, R^6 and R^n are as defined above).

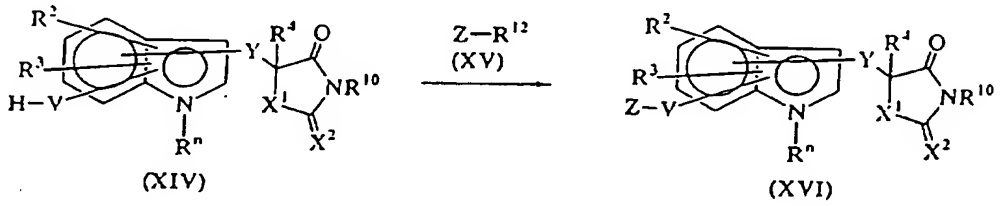
A compound of the formula (I-2c) (X^1=S, X^2=NH), can be converted into a compound of the formula (I-2d) (X^1=S, X^2=O) by hydrolyzing an imino group at the 2-position of

thiazolidine by a well known method.

This reaction is conducted usually in the presence of water and an acid in an appropriate organic solvent. Examples of the solvent include usually alcohols, cellosolves, aprotic polar organic solvents, ethers and alkoxy alkanes, preferably methanol, ethanol, methoxyethanol, sulfolane, dioxane and dimethoxyethane. Examples of the acid include inorganic acids (such as hydrochloric acid, sulfuric acid and hydrobromic acid), and these materials are selected optionally depending on the reactivity of the aimed reaction.

This reaction is conducted usually at a temperature in the range of from 50°C to a boiling point of a solvent used in the reaction, preferably from 80°C to 150°C. The reaction time is usually from 0.5 to 30 hours.

Process 8



(XIV) (XVI)

(wherein R^2, R^3, R^4, R^{10}, R^{12}, X^1, X^2, Y, V and Z are as defined above).

An indole compound (R^1=-V-Z) of the formula (XVI) can also be obtained by reacting a compound of the formula (XV) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIV) by a

nucleophilic substitution reaction. The compound of the formula (XIV) is preferably protected by substituting hydrogen of R^{10} with an appropriate substituent (such as Tr: trityl).

This reaction is usually conducted in an appropriate organic solvent in the presence of base. Examples of the solvent used include aprotic polar organic solvents, ethers, aromatic hydrocarbons, hydrogenated hydrocarbons, alkoxyalkanes, acetonitrile, and the like.

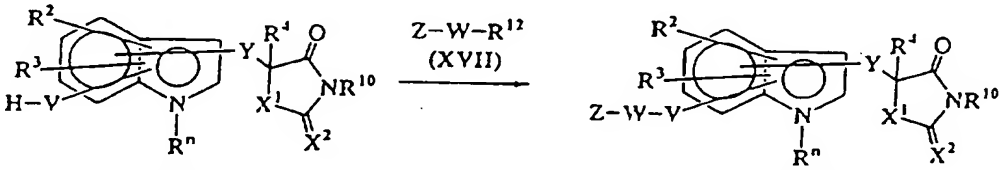
Examples of the base thus used include organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine), Acid Captor H: 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one and Acid Captor 9M: 9-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one), metal alkoxides (such as sodium methoxide, sodium ethoxide, lithium isopropoxide and potassium t-butoxide), inorganic alkali metal salts (such as sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydride, sodium acetate and potassium acetate), and alkali metal amides (such as sodium amide). These materials are selected appropriately depending on the reactivity of the aimed reaction.

This reaction is conducted usually at a temperature

ranging from -20°C to a boiling point of the solvent used, preferably from 20°C to 150°C, for from 0.5 to 30 hours.

Among compounds thus obtained, the one having a protecting group on the thiazolidine ring as represented by the formula (XVI), can be led to a compound of the formula (I) either in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts in "Protective Groups in Organic Synthesis" (1991) or deprotecting the amide group at the 3-position of the thiazolidine ring by the method described in Process 5.

Process 9



(XIV) (XVIII)

(wherein R^2, R^3, R^4, R^{10}, R^{12}, R^n, X^1, X^2, Y, V, W and Z are as defined above).

An indole compound (R^1=-V-W-Z) of the formula (XVIII), can also be obtained by reacting a compound of the formula (XVII) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIV) by nucleophilic substitution reaction. The compound of the formula (XIV) is preferably protected by substituting hydrogen of R^{10} with an appropriate substituent (such as Tr: trityl).

Among compounds of the formula (I), a compound

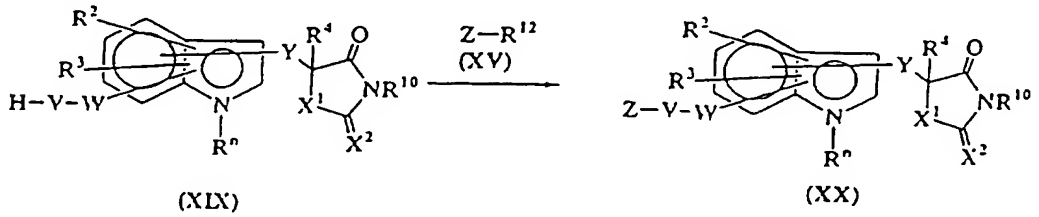
wherein R^1 is -V-W-Z and W is $COCH_2$, can be obtained by using a compound of Z-$COCH_2$-Hal (W=$COCH_2$, R^{12}=Hal, Z and Hal are substituents explained above). Such a compound is well known and is commercially available, or can be obtained by a well known method (for example, British Laid Open Patent Publication No. 1107677 discloses a compound wherein Z is pyrrole, Japanese Unexamined Patent Publication No. 85372/1986 discloses a compound wherein Z is oxazole or thiazole and U.S. Patent No. 4,167,626 discloses a compound wherein Z is triazole). Also, such a compound can be obtained by halogenating Z-$COCH_3$ (for example, "Bull. Soc. Chim. Fr., p. 1760 (1973)" discloses a compound wherein Z is furan, "Tetrahedron, 29(2), p. 413 (1973)" discloses a compound wherein Z is thiophene, "J. Heterocyclic Chem., 27(5), p. 1209 (1990)" discloses a compound wherein Z is pyrrole, "Bull. Soc. Chim. Fr., p. 540 (1988)", "Bull. Soc. Chim. Fr., p. 318 (1987)", "J. Heterocyclic Chem., 23(1), P. 275 (1986)", "Arch. Pharm., 316(7), p. 608 (1983)" and "Synlett., (7), p. 483 (1991)" disclose a compound wherein Z is pyrazole, "J. Heterocyclic Chem., 17(8), p. 1723 (1980)" discloses a compound wherein Z is imidazole, and "J. Chem. Soc. C(20), p. 2005 (1976)" and "Heterocycles, 26(3), p. 745 (1987)" disclose a compound wherein Z is triazole) as a starting material by means of an appropriate well known halogenation method (e.g. a method disclosed in Japanese Unexamined Patent Publication No. 85372/1986). Also,

such a compound can be obtained by subjecting Z-CO_2R' (R'=lower alkyl or substituted or unsubstituted benzyl) (for example, "Z. Chem., 9(1), p. 22 (1969)" and "Synth. Commun., 20(16), p. 2537 (1990)" disclose a compound wherein Z is thiophene, "J. Org. Chem., 55(15), p. 4735 (1990)" and "Chem. Pharm. Bull., 17(3), p. 582 (1969)" disclose a compound wherein Z is pyrrole, European Laid Open Patent Publication No. 506194 discloses a compound wherein Z is imidazole, and "Chem. Ber., 117(3), p. 1194 (1984)" discloses a compound wherein Z is pyrazole or triazole) as a starting material to an appropriate well known reduction-oxidation reaction (for example, reduction by diisobutyl aluminum hydride and then oxidation by manganese dioxide) to obtain Z-CHO, and further by converting the product thus obtained to Z-$COCH_2$-hal by an appropriate method (e.g. a method disclosed in "Tetrahedron Letters, p. 4661 (1972)").

This reaction can be conducted in the same manner as in the Process 8.

Among compounds thus obtained, the one having a protecting group on the thiozolidine ring as represented by the formula (XVIII), can be led to a compound of the formula (I) either in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts in "Protective Groups in Organic Synthesis" (1991) or deprotecting the amide group at the 3-position of the thiazolidine ring by the method described in Process 5.

Process 10



(XIX) (XX)

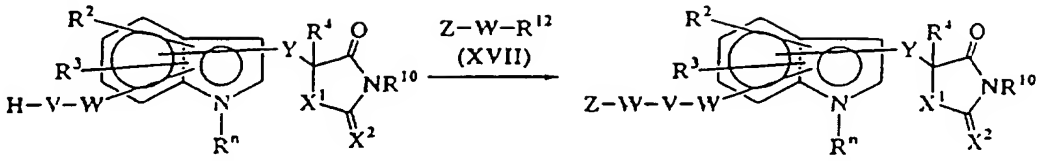
(wherein R^2, R^3, R^4, R^{10}, R^{12}, R^n, X^1, X^2, Y, V, W and Z are as defined above).

An indole compound (R^1=-W-V-Z) of the formula (XX) can also be obtained by reacting a compound of the formula (XV) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIX) by nucleophilic substitution. The compound of the formula (XIX) is preferably protected by substituting hydrogen of R^{10} with an appropriate substituent (such as Tr: trityl).

This reaction can be conducted in the same manner as in the above Process 8.

Among the compounds thus obtained, the compound having a protective group introduced into a thiazolidine ring part of the formula (XX) can be converted into a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts "Protective Groups in Organic Synthesis" (1991) or the method disclosed in the Process 5.

Process 11



(XIX) (XXI)

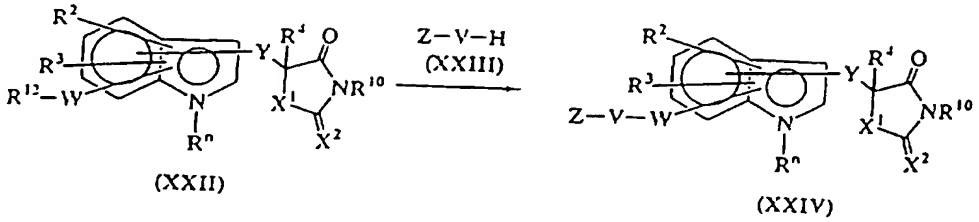
(wherein R^2, R^3, R^4, R^{10}, R^{12}, R^n, X^1, X^2, Y, V, W and Z are as defined above).

An indole compound (R^1=-W-V-W-Z) of the formula (XXI) can also be obtained by reacting a compound of the formula (XVII) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIX). The compound of the formula (XIX) is preferably protected by substituting hydrogen of R^{10} with an appropriate substituent (such as Tr: trityl).

This reaction can be conducted in the same manner as in the above Process 8.

Among the compounds thus obtained, the compound having a protective group introduced into a thiazolidine ring part of the formula (XXI) can be converted to a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Green, P.G.M. Wuts "Protective Groups in Organic Synthesis" (1991) or the method disclosed in the above Process 5.

Process 12



(XXII) (XXIV)

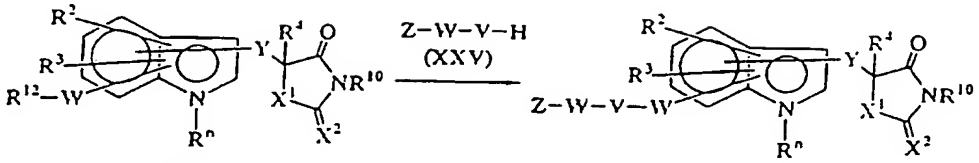
(wherein R^2, R^3, R^4, R^{10}, R^{12}, R^n, X^1, X^2, Y, V, W and Z are as defined above).

An indole compound (R^1=-W-V-Z) of the formula (XXIV) can also be obtained by reacting an indole compound of the formula (XXII) with a hydroxyl group, a thiol group or an amino group of a compound of the formula (XXIII) by nucleophilic substitution. The compound of the formula (XXII) is preferably protected by substituting hydrogen of R^{10} with an appropriate substituent (such as Tr: trityl).

This reaction can be conducted in the same manner as in the above Process 8.

Among the compounds thus obtained, a compound having a protective group introduced into a thiazolidine ring part of the formula (XXIV) can be converted to a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts "Protective Groups in Organic Synthesis" (1991) or the method disclosed in the above Process 5.

Process 13



(XXII) (XXVI)

(wherein R^2, R^3, R^4, R^{10}, R^{12}, R^n, X^1, X^2, Y, V, W and Z are as defined above).

An indole compound (R^1=-W-V-W-Z) of the formula (XXVI) can also be obtained by reacting an indole compound of the formula (XXII) with a hydroxyl group, a thiol or an amino group of a compound of the formula (XXV). The compound of the formula (XXII) is preferably protected by substituting hydrogen of R^{10} with an appropriate substituent (such as Tr: trityl).

This reaction can be conducted in the same manner as in the above Process 8.

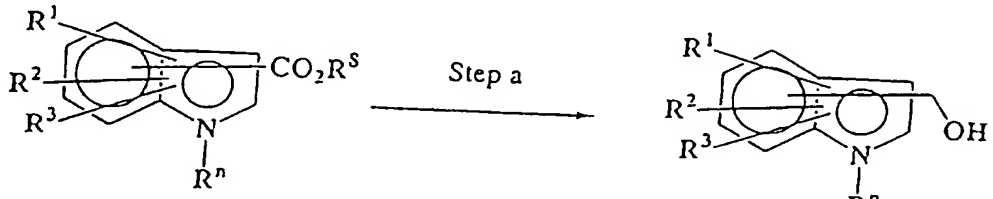
Among the compounds thus obtained, a compound having a protective group introduced into a thiazolidine ring part of the formula (XXVI) can be converted to a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts "Protective Groups in Organic Synthesis" (1991) or the method disclosed in the above Process 5.

Now, the processes for producing intermediates useful for the preparation of the compounds of the present

invention will be described hereinafter.

Method for preparing intermediate (III)

Synthesis Route 1 [Step a]



(IV) (III)

(wherein R^1, R^2, R^3 and R^n are as defined above, and R^8 is a hydrogen atom, a C_1-C_4 alkyl group, a phenyl group or a benzyl group).

A hydroxymethylindole (intermediate (III)) is available by using a commercial available reagent or by reducing a carboxyl indole of the formula (IV) or an alkoxycarbonylindole.

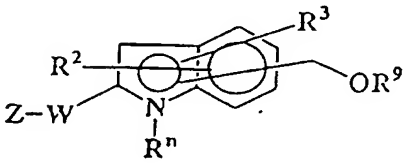
The step of synthesizing the compound of the formula (III) can be conducted by using a well known appropriate reducing agent (e.g. metal hydride complex compounds such as LAH: lithium aluminum hydride, SAH: sodium aluminum hydride, sodium triethoxyaluminum hydride, Red-Al: sodium bis(2-methoxyethoxy) aluminum hydride, SBH: sodium borohydride and LBH: lithium borohydride, and metal hydride compounds such as DIBAH: diisobutyl aluminum hydride, and catalytic hydrogenation using CuBaCrO as a catalyst).

Synthesis Route 2 Introduction of substituent R^1 into the 2-positon of indole

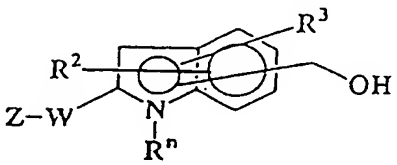
(III)
(R^1=H , R^n=H)

(VII)
(R^1=H , R^n=H)

Step b
Z—A
(VIII)



(VII)
(R^1=Z–W– , R^n=H)



(III)
(R^1=Z–W– , R^n=H)

(wherein R^1, R^2, R^3, R^n, W and Z are as defined above, and R^9 is a protecting group (such as t-butyldimethylsilyl group) of a primary hydroxymethyl group).

Among hydroxymethyl indole compounds of the formula (III), a compound having a hydrogen atom at the 2-position of an indole ring can get a carbon functional group: R^1 (Z-W-, Z-V-W-, Z-W-V- and Z-V-) introduced at the 2-position by means of the following method.

(Protection of hydroxymethyl group)

In this synthesis route, a compound (VII) can be obtained by protecting a primary hydroxymethyl group of hydroxymethyl indole of the formula (III) by means of a well known method. For example, protection of these alcohols can be conducted in accordance with the method disclosed by T.W. Greene, P.G M. Wuts in " Protective Groups in Organic Synthesis" (1991). A protective group: R^9 is preferably stable under basic conditions in the following step, examples of which include a substituted silyl group (such as trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl and t-butylmethoxyphenylsilyl), a substituted acyl group (such as chloroacetyl, dichloroacetyl, trichloroacetyl, fluoroacetyl, difluoroacetyl, trifluoroacetyl and

pivaloyl), benzoyl, a substituted alkoxycarbonyl group (such as methoxycarbonyl, ethoxycarbonyl, t-butyloxycarbonyl and i-butyloxycarbonyl), and the like, particularly preferably triisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl and the like. When the protective group is t-butyldimethylsilyl, this reaction is conducted by using t-butyldimethylsilyl chloride in dimethylformamide in the presence of imidazole at room temperature in accordance with J. Amer. Chem. Soc., vol. 94, P 6190 (1972).

(Step b)

In Step b, at the 2-position of the indole ring of the compound (VII) thus obtained, a carbon functional group: Z-W-, Z-V-W- or Z-V- can be introduced in accordance with the method disclosed by A. R. Kartitzky, "Tetrahedron Letters" vol. 26(48), P5935 (1985).

A compound of the formula (VIII) means an electrophilic reagent which can be reacted with an indole ring metalated in step b. Examples of a substrate usable in such a reaction are illustrated below. For example, in the case of synthesizing a compound of the formula (VII) wherein W is $-CH_2-$ (R^d=H, R^e=H, m=1), a compound of the formula Z-A (A is $-CH_2-B$ (B is a leaving group in this reaction, such as a chlorine atom, a bromine atom, an iodine atom, methanesulfonyl, benzenesulfonyl and p-toluenesulfonyl)) can be employed. When synthesizing a compound of the formula (VII) wherein W is $-C(=O)-$ (R^d

and R^e together form an oxo group and m=1), a compound of the formula Z-A (A is -C(=O)-B (B is a leaving group in this reaction, such as OH, OLi, ONa, OK, a chlorine atom, a bromine atom, an iodine atom and methoxymethylamino, preferably OK, a chlorine atom, a bromine atom and methoxymethylamino)) can be employed. In the case of synthesizing a compound of the formula (VII) wherein W is -C(OH)H- (R^d=H, R^e=OH, m=1), a compound of the formula Z-A (A is -CHO) can be employed. In the case of synthesizing a compound of the formula (VII) wherein W is -C(OH)R^d- (R^d=Me or Ph, R^e=OH, m=1), a compound of the formula Z-A (A is -C=O)-R^d (R^d=M^e or Ph)) can be employed. In the case of synthesizing a compound of the formula (VII) wherein V is -S-, a compound of the formula Z-A (A is -S-S-Z) can be employed.

When synthesizing a compound of the formula (VII) wherein V is $-SO_2-$, a compound of the formula Z-W-A or Z-A (A is SO_2-B (B is an eliminated group in this reaction, such as a halogen atom, preferably a chlorine atom)) can be employed. When synthesizing a compound of the formula (VII) wherein W-V is CO-NH, a compound of the formula Z-A (A is -N=C=O) can be employed.

A compound of the formula (VIII) may be a commercially available reagent or can be synthesized by a well known method.

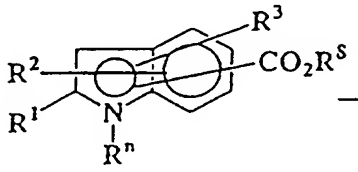
In this case, lithium tetrahydrofuran, sodium hydroxide, potassium hydroxide, lithium, sodium,

potassium, zinc, magnesium or copper, preferably s-butyl lithium or t-butyl lithium is used in an inert gas atmosphere such as nitrogen or argon. For example, in the case of using t-butyl lithium, the reaction is conducted at a temperature of from -100°C to 100°C, preferably at -78°C, for 1 to 2 hours, and the reaction with a compound of the formula (VIII) is then conducted at -78°C. Thereafter, the reaction temperature is returned to room temperature, and a saturated ammonium chloride aqueous solution is added thereto, and the reaction mixture is heated at 80°C-120°C to obtain a compound of the formula (VII) or to isolate a carboxylic acid compound (VII) R^n=COOH by recrystallization, which is then heated at 80°C-200°C to conduct decarboxylation.

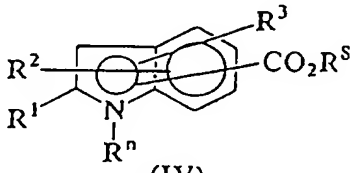
(Deprotection of hydroxylmethyl group)

Deprotection of a primary hydroxylmethyl group is conducted by means of a well known method. For example, deprotection of these alcohols is conducted in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts "Protective Groups in Organic Synthesis" (1991) to obtain a compound (III) wherein R^1 is introduced at the 2-position. When R^9 is t-butyldimethylsilyl, this reaction is conducted by using tetra-n-butylammonium fluoride in THF: Tetrahydrofuran at 0°C-30°C in accordance with the method disclosed in J. Amer. Chem. Soc., vol. 94, P6190(1972).

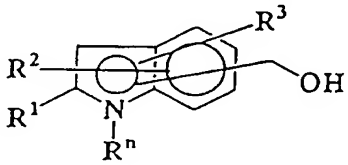
Synthesis Route 3 Introduction of substituent R^1 at the 2-position of indole



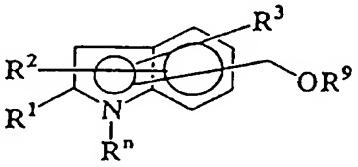
(IV)
(R^1=H , R^n=H)



(IV)
(R^1=H , R^n≠H)



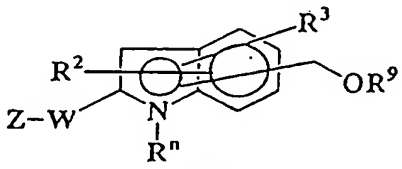
(III)
(R^1=H , R^n≠H)



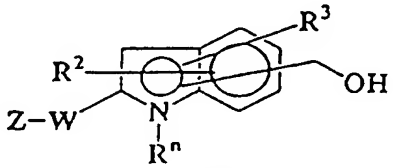
(VII)
(R^1=H , R^n≠H)

Step C

Z—A
(VIII)



(VII)
(R^1=Z-W- , R^n≠H)



(III)
(R^1=Z-W- , R^n≠H)

(wherein R^1, R^2, R^3, R^8, R^9, R^n, W and Z are as defined above).

Among alkoxycarbonyl indoles of the formula (IV), a compound having an indole ring having hydrogen at the 1-position and the 2-position can be converted to the corresponding hydroxymethyl indole (compound (III)) by introducing a carbon functional group: R^1 (Z-W-) by means of the following method.

The alkoxycarbonyl indole of the formula (IV) used may be a commercially available reagent or may be obtained by esterifying indole carboxylic acid as a starting material by a well known method.

(Displacement of R^n substituent)

In this synthesis route, firstly a substituent: R^n ($\neq$H) is introduced at the 1-position of an indole ring of alkoxycarbonyl indole (IV). Examples of R^n include a C_1-C_7 alkyl group, a C_1-C_4 alkoxymethyl group, a C_1-C_4 alkylaminomethyl group, a carboxyl group, a C_1-C_4 alkoxycarbonyl group, a C_1-C_4 alkylaminocarbonyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkoxyalkylmethyloxy group, an alkylsulfonyl group and an aryl sulfonyl group, preferably methyl, methoxymethyl, dimethylaminomethyl, carboxyl, t-butyloxycarbonyl, methylcarbamoyl, methoxy, methoxymethyloxy, mesyl, benzene sulfonyl, p-toluenesulfonyl, p-methoxybenzenesulfonyl, p-fluorobenzenesulfonyl and p-chlorobenzenesulfonyl, more preferably benzene sulfonyl. When R^n is $PhSO_2$-, this

reaction is conducted by using benzenesulfonyl chloride, sodium hydride and n-butyl lithium in dimethylformamide at 0°C- 100°C in accordance with the method disclosed by R.J. Sundberg, "J. Org. Chem." vol. 38(19), P3324 (1973).

(Reduction of alkoxycarbonyl group)

The alkoxycarbonyl group of the compound (IV) thus obtained is reduced by using an appropriate reducing agent such as DIBAL: diisobutylaluminium hydride and LAH: lithium aluminum hydride by means of a well known method to obtain the corresponding hydroxymethyl indole (compound (III)). This reaction is conducted, for example, in THF at 0°C-50°C.

(Protection of hydroxymethyl group)

The primary hydroxymethyl group of the hydroxymethyl indole (compound (III)) is protected by means of a well known method to obtain a compound (VII). A protective group: R^9 should be preferably stable under basic conditions in the following step, and the same protective group as used in Synthesis Route 1 can be used. For example, when a t-butyldimethylsilyl group is used, a protective group can be introduced in the same manner as in Synthesis Route 1.

(Step c)

In the compound (VII) thus obtained, a carbon functional group R^1 can be introduced at the 2-position of the indole ring in accordance with the method disclosed by R.J. Sundberg, "J. Org. Chem.", vol. 38

(19), P3324 (1973).

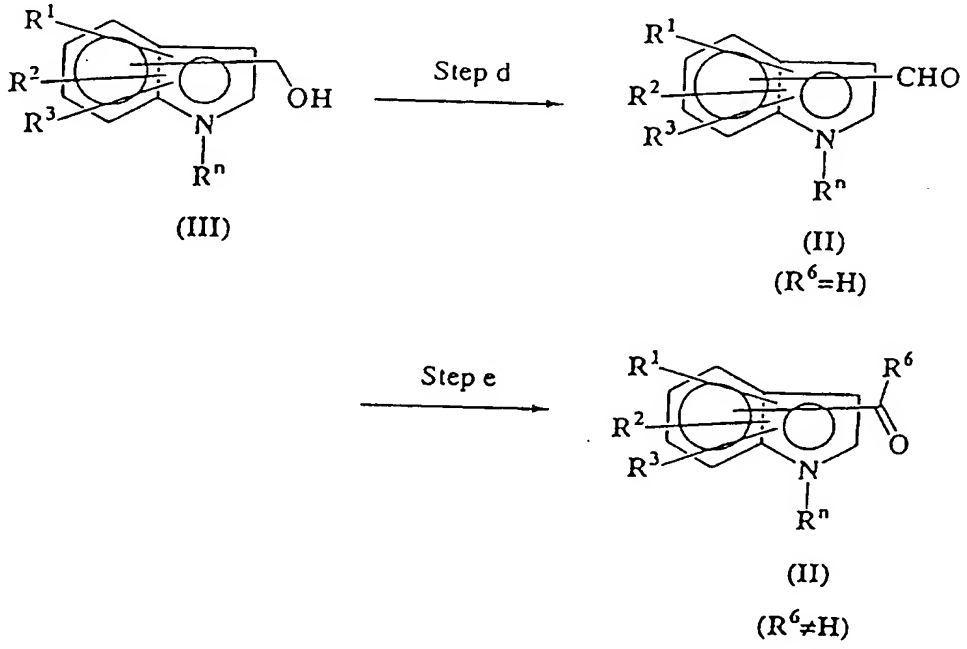
In this reaction, a compound of the formula (VII) is reacted with a base to anionize the 2-position under an inert gas atmosphere such as nitrogen or argon in an aprotic organic solvent such as tetrahydrofuran, ether, isopropyl ether, n-pentane, i-pentane, cyclopentene, n-hexane, cyclohexane, HMPA: hexamethylphosphoric triamide, HMPT: hexamethylphosphorous triamide, N,N,N',N'-tetramethylethylenediamine, dioxane, dimethylsulfoxide or dimethylformamide. Examples of the base used include n-butyl lithium, s-butyl lithium, t-butyl lithium, phenyl lithium, methyl lithium, LDA: lithium diisopropyl amide, potassium bis(trimethylsilyl)amide, calcium hydride, sodium hydride, potassium hydride, potassium carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium, sodium, potassium, zinc, magnesium or copper, preferably n-butyl lithium, s-butyl lithium, t-butyl lithium or LDA. For example, when t-butyl lithium is used, the reaction is conducted at a temperature of from -100°C to 100°C, preferably from -78°C to 0°C, for 10 to 120 minutes, and then the reaction with a compound of the formula (VIII) is conducted to introduce a carbon functional group at the 2-positon of the indole ring. A compound of the formula (VIII) may be a commercially available reagent or may be synthesized in the same manner as above.

(Deprotection of hydroxymethyl group)

The deprotection of a primary hydroxymethyl group is conducted by means of a well known method to obtain a compound (III) having R^1 introduced at the 2-position. When R^9 is t-butyldimethylsilyl, this reaction is conducted under the same conditions as in Synthesis Route 1.

Method for preparing intermediate (II)

Synthesis Route 1



(wherein R^1, R^2, R^3, R^6 and R^n are as defined above).

A carbonyl indole of the formula (II) is a well known compound or can be obtained by oxidizing a hydroxymethyl indole of the formula (III). This step is conducted by using an appropriate oxidizing agent (such as manganese dioxide, PCC: pyridiniumchlorochromate, PDC:

pyridiniumdichromate, DDQ: dichlorodicyanobenzoquinone, chloranil, Swern oxidizing agent: oxalyl chloride-dimethylsulfoxide-tertiary amine or sulfur trioxide-pyridine complex).

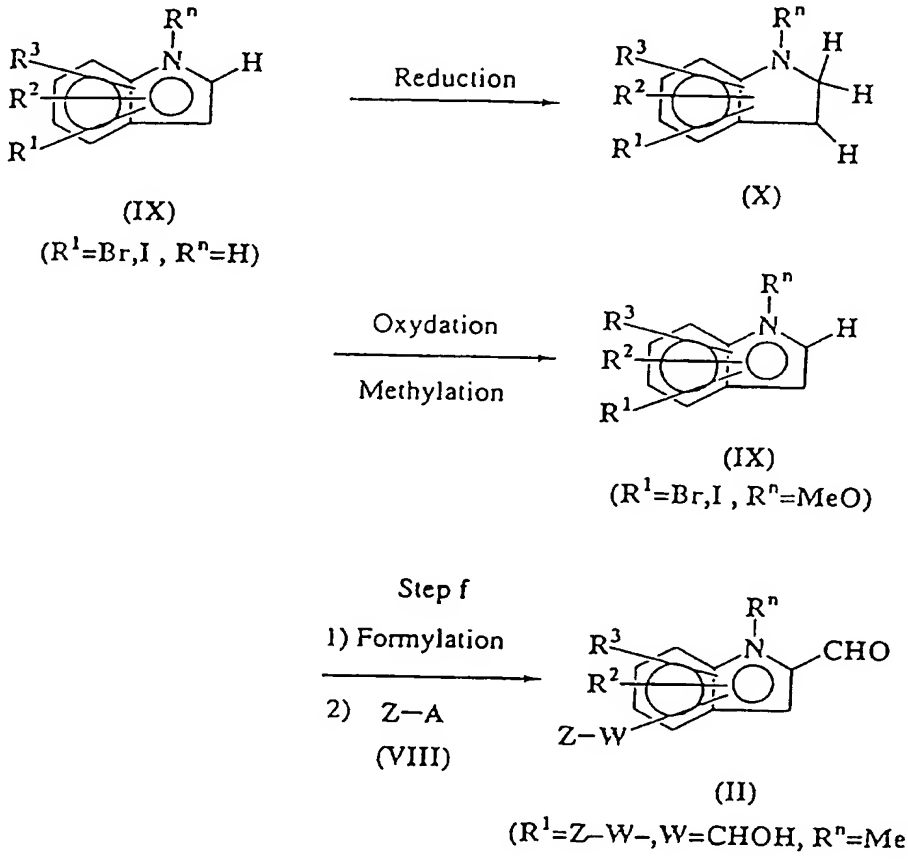
An example of using pyridine chromic acid complex as an oxidizing agent is disclosed in Japanese Examined Patent Publication No. 34986/1974.

A formylindole of the formula (II) (R^6=H) obtained by the above method can be converted to a carbonylindole of the formula (II) (R^6≠H) by alkylating the formyl group with an appropriate alkylating agent.

This step can be conducted by the method using diazomethane as disclosed in "Tetrahedron Letters" P955 (1963) and "Chem. Ber." vol. 40, P479 (1907), the method using alkyl halide as disclosed in "Synth. Commun." vol. 14(8), P743 (1984) or the method using alkyl lithium as disclosed in "J. Org. Chem." vol. 30, P226 (1965).

Synthesis Route 2

Introduction of substituent R^1 and formylation at the 2-positon of indole



(IX)
(R^1=Br,I , R^n=H)

(X)

(IX)
(R^1=Br,I , R^n=MeO)

(II)
(R^1=Z–W–,W=CHOH, R^n=MeO)

(wherein R^1, R^2, R^3, R^n, W and Z are as defined above).

Among formylindoles of the formula (II) (R^6=H), a compound having a formyl group at the 2-positon of an indole ring and having a carbon functional group R^1 at the 4-, 5-, 6- or 7-position can be synthesized by the following method.

A carbon functional group: R^1 can be introduced in the indole nucleus by protecting a nitrogen atom at the

1-position of haloindole of the formula (IX) with a lower alkoxy group, particularly a methoxy group, conducting formylation at the 2-position, conducting metalation of the haloindole in the presence of a strong base and then reacting with an aldehyde compound of the formula (XI).

(Reduction of indole ring)

A haloindole (IX) used as a starting material has a hydrogen atom at the 1-positon and a halogen atom at the 4-, 5-, 6- or 7-position. The halogen atom is preferably bromine or iodine, more preferably bromine, and the haloindole (IX) used is a commercially available reagent or can be synthesized by a well known method. The haloindole (IX) can be converted into the corresponding indoline (compound (X)) by reducing at the 2- and 3-positions of the indole ring, for example, by the method disclosed in "J. Amer. Chem. Soc. " vol. 96, P7812 (1974).

(Synthesis of methoxyindole by oxidation and methylation of indoline)

The indoline (compound (X)) can be converted into the corresponding 1-methoxyhaloindole (compound (IX)) by conducting oxidation and methylation at the 2-, 3- and 1-positions in accordance with the method disclosed in Japanese Unexamined Patent Publication No. 31257/1991 (M. Somei). This reaction is conducted by oxidizing with a 30% hydrogen peroxide aqueous solution in a methanol/water mixture solvent in the presence of

disodium tungstate dihydrate as a catalyst at 0°C and then methylating with diazomethane or dimethylsulfuric acid: potassium carbonate at room temperature.

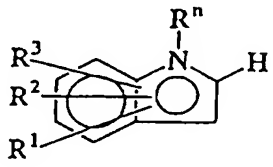
(Step f)

1-methoxyhaloindole (compound (IX)) can be converted to the aimed formylindole (compound (II)) by conducting formylation at the 2-positon and then reacting with compound (VIII) in accordance with the method disclosed in "Heterocycles" by M. Somei, vol. 132, P221 (1991).

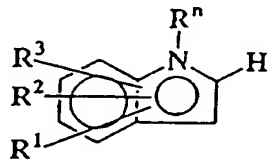
The 2-position of 1-methoxyhaloindole is anionized by reacting with a base under an inert gas atmosphere such as nitrogen or argon in an aprotic organic solvent such as tetrahydrofuran, ether, isopropyl ether, n-pentane, i-pentane, cyclopentane, n-hexane, cyclohexane, HMPA: hexamethylphosphoric triamide, HMPT: hexamethylphosphorous triamide, N,N,N',N'-tetramethylethylene diamine, dioxane, dimethylsulfoxide or dimethylformamide. Examples of such a base include n-butyl lithium, s-butyl lithium, t-butyl lithium, phenyl lithium, methyl lithium, LDA: lithium diisopropyl amide, potassium bis(trimethylsilyl)amide, calcium hydride, sodium hydride, potassium hydride, potassium carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium, sodium, potassium, zinc, magnesium and copper, preferably phenyl lithium, n-butyl lithium and LDA. For example, when phenyl lithium is used, the reaction is conducted for 10-120 minutes by lithium-modifying the 2-

position in tetrahydrofuran at a temperature of from -100°C to 100°C, preferably from -78°C to 0°C, and reaction with N,N'-dimethylformamide, N,N'-methoxymethylformamide is then conducted for 5 to 120 minutes. Thereafter, the 5-position is anionized by further reacting with a base at a temperature of from -100°C to 100°C, preferably from -78°C to 0°C. Examples of the base used include n-butyl lithium, s-butyl lithium, t-butyl lithium, phenyl lithium, methyl lithium, LDA: lithium diisopropylamide, potassium bis(trimethylsilyl)amide, calcium hydride, sodium hydride, potassium hydride, potassium carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium, sodium, potassium, zinc, magnesium and copper, preferably s-butyl lithium and t-butyl lithium. For example, when t-butyl lithium is used, after reacting for 10 to 120 minutes, reaction with the compound of the formula (VIII) is conducted to obtain the aimed formyl indole (compound (II)).

Synthesis Route 3

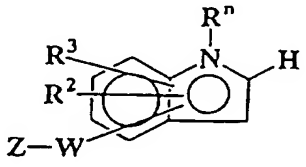


(IX)
(R^1=Br,I , R^n=H)

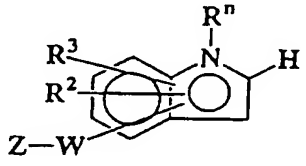


(IX)
(R^1=Br,I , R^n=$Si(iPr)_3$)

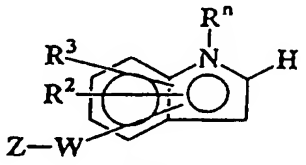
Step g
Z—A
(VIII)



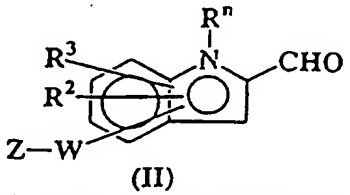
(IX)
(R^1=Z-W-,W=CHOH, R^n=$Si(iPr)_3$)



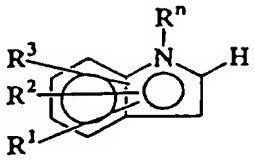
(IX)
(R^1=Z-W-,W=CHOH, R^n=H)



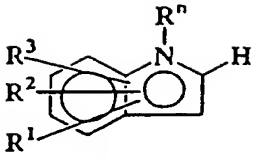
(IX)
(R^1=Z-W-,W=$CHOSiMe_2Bu^t$, R^n=H)



(II)
(R^1=Z-W-,W=$CHOSiMe_2Bu^t$, R^n=H)

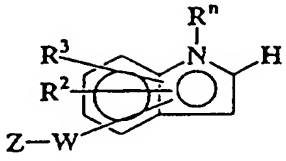


(IX)
(R^1=Br,I , R^n=H)

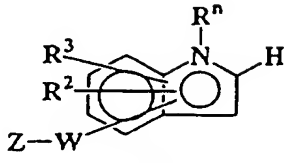


(IX)
(R^1=Br,I , R^n=Si(iPr)$_3$)

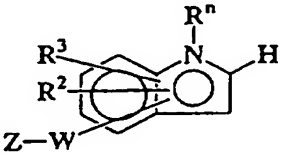
Step g
Z—A
(VIII)



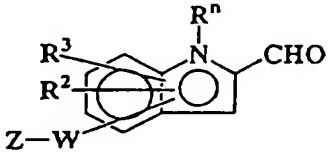
(IX)
(R^1=Z-W-,W=CHOH, R^n=Si(iPr)$_3$)



(IX)
(R^1=Z-W-,W=CHOH, R^n=H)



(IX)
(R^1=Z-W-,W=CHOSiMe$_2$Bu^t, R^n=H)



(II)
(R^1=Z-W-,W=CHOSiMe$_2$Bu^t, R^n=H)

(wherein R^1, R^2, R^3, R^n, W and Z are as defined above).

Among formylindoles of the formula (II) (R^6=H), an indole having a formyl group at the 2-position of the indole ring and having a carbon functional group: R^1 at the 4-, 5-, 6- or 7-position can be synthesized by the following method.

After protecting a nitrogen atom at the 1-position of a haloindole of the formula (IX) with a substituted silyl group, the haloindole is subjected to metalation in the presence of a strong base and was reacted with an aldehyde compound of the formula (VIII) to introduce a carbon functional group into the indole ring. Thereafter, the silyl group at the 1-position is deprotected and the 2-position is formylated to obtain a formylindole (intermediate (II)).

The haloindole (IX) (R^1=Br, I, R^n=H) used as a starting material has a hydrogen atom at the 1-position and a halogen atom at the 4-, 5-, 6- or 7-position. The halogen atom is preferably bromine or iodine, more preferably bromine and the haloindole used may be a commercially available reagent or may be prepared by a well known method.

(Introduction of substituent R^n)

An appropriate substituent is introduced into the haloindole (IX) by a well known method. Examples of the substituent include a substituted silyl group, a C_1-C_7 acyl group, a C_1-C_4 alkoxycarbonyl group and a C_1-C_4

alkylaminocarbonyl group, preferably pivaloyl, t-butyl oxycarbonyl, t-butyl carbamoyl, triisopropylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl, more preferably triisopropylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl.

(Step g)

The 5-position of the compound of the formula (IX) (R^1=Br, I, R^n=H) is anionized by reacting with a base under an inert gas atmosphere such as nitrogen or argon in an aprotic organic solvent such as tetrahydrofuran, ether, isopropyl ether, n-pentane, i-pentane, cyclopentane, n-hexane, cyclohexane, HMPA: hexamethylphosphoric triamide, HMPT: hexamethylphosphorous triamide, N,N,N',N'-tetramethylethylene diamine, dioxane, dimethylsulfoxide or dimethylformamide, preferably tetrahydrofuran or ether. Examples of the based used include n-butyl lithium, s-butyl lithium, t-butyl lithium, phenyl lithium, methyl lithium, LDA: lithium diisopropyl amide, potassium bis(trimethylsilyl)amide, calcium hydride, sodium hydride, potassium hydride, potassium carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium, sodium, potassium, zinc, magnesium and copper, preferably n-butyl lithium, s-butyl lithium, t-butyl lithium and methyl lithium. For example, when t-butyl lithium is used, the reaction is conducted in ether at a temperature of from -100°C to 100°C, preferably -78°C to

0°C, for 10 to 120 minutes, and the reaction product is further reacted with a compound of the formula (VIII) to obtain a compound (IX) (R_1=Z-W-, W=CHOH, R^n=Si $(iPr)_3$). (Removal of R^n substituent)

A compound of the formula (IX) (R^1=Z-W-, W=CHOH, R^n=Si$(iPr)_3$) can be converted to a compound of the formula (IX) (R^1=Z-W-, W=CHOH, R^n=H) by reacting with tetra-n-butylammonium fluoride in tetrahydrofuran or ether at room temperature.

(Protection of hydroxy group)

A compound of the formula (IX) (R^1=Z-W-, W=CHOH, R^n=H) can be converted to a compound of the formula (IX) (R^1=Z-W-, W=C(H)OSiMe_2t-Bu, R^n=H) by reacting with tertiary butyldimethylsilyl chloride in the presence of imidazole in dimethylformamide.

(Formylation at the 2-position of indole ring)

A compound of the formula (IX) (R^1=Z-W-, W=C(H)OSiMe_2t-Bu, R^n=H) can be converted into a formylated product (II) by the method disclosed in "J. Am. Chem. Soc." of A. R. Katritzky, vol. 108, P 6808 (1986).

Synthesis Route 4

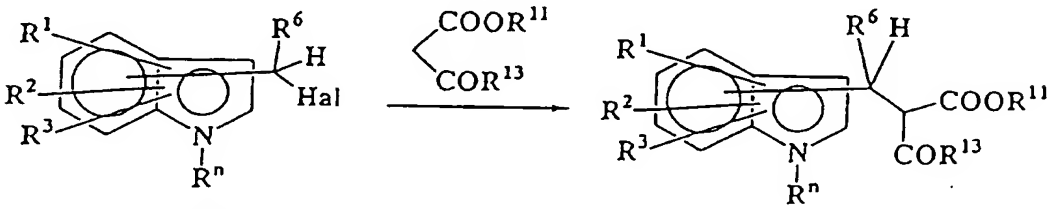
(III) (II) (R^6=H)

(wherein R^1, R^2, R^3 and R^n are as defined above).

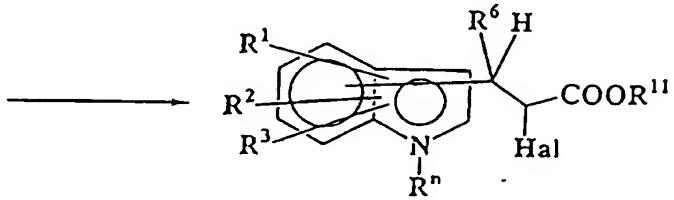
The formylated product (II) can be obtained by reducing a cyano group of an indole of the formula (XIII). This step can be conducted by using an appropriate reducing agent (such as Raney nickel, nickel, sodium aluminum hydride, sodium triethoxyaluminum hydride, diisobutylaluminium hydride and tin chloride (II)).

An example of reducing an indole (XIII) by using Raney nickel is described in Japanese Unexamined Patent Publication No. 151172/1986.

Method for preparing intermediate (XII)



(VI) (XI)



(XII)

(wherein R^1, R^2, R^3, R^6, R^{11}, Z and Hal are as defined above, and R^{13} is OR^{11} (R^{11} is as defined above) or C_1-C_3 alkyl such as methyl, ethyl, n-propyl and i-propyl).

A halocarboxylic acid ester of the formula (XII) can be obtained by reacting a halomethylindole of the formula (VI) with a malonic acid ester or a lower acylacetic acid ester by a well known method to obtain a compound of the formula (XI) and halogenating the compound of the formula (XI) thus obtained.

The halomethylindole of the formula (VI) can be synthesized by the method disclosed in "Org. Prep. Proced. Int." vol. 25, P249 (1993). Thus, the halomethylindole of the formula (VI) can be obtained by halogenating a hydroxymethylindole of the formula (III) with an appropriate halogenating agent (such as $SOCl_2$, $POCl_3$, PCl_5, HCl, $SnCl_4$, HBr, PBr_3, Br_2, $POBr_3$, methanesulfonic acid chloride, p-toluenesulfonic acid chloride, N-bromosuccinimide-triphenylphosphine and N-chlorosuccinimide-triphenylphosphine).

Among compounds of the formula (XI), a compound wherein R^{13} is C_1-C_3 alkyl, can be obtained by reacting a halomethylindole of the formula (VI) with a lower acylacetic acid ester such as methyl acetoacetate or ethyl acetoacetate in the presence of an appropriate base (such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium amide, potassium amide, diisopropylamide, butyl lithium, metallic sodium, potassium carbonate, sodium hydride, potassium hydride and calcium hydride) in accordance with the method disclosed in "J. Amer. Chem. Soc." vol 64, P435 (1942).

Among compounds of the formula (XII), a compound wherein R^{13} is OR^{11}, can be obtained by reacting a halomethylindole of the formula (VI) with a malonic acid ester such as diethyl malonate or di-t-butyl malonate in the presence of such a base as mentioned above, in accordance with the method disclosed in "J. Amer. Chem. Soc." vol 74, P831 (1952).

The step for preparing a compound of the formula (XII) is conducted by using an appropriate halogenating agent (such as bromine or N-chlorosuccinimide) in the presence of an appropriate base (such as potassium hydroxide, sodium methoxide or potassium carbonate) in accordance with the method disclosed in "J. Amer. Chem. Soc." vol 71, P3107 (1949) or "Tetrahedron Letters" vol. 28, P5505 (1987).

Also, a compound of the formula (XII) can be obtained by reacting a halomethylindole of the formula (VI) with a diazoacetic acid ester in the presence of a copper catalyst in accordance with the method disclosed in "Zur. Russ. Fiz-Chim." vol. 21, P851 (1951).

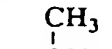
Among the above-mentioned compounds (II), (III), (VII) and (IX), the compound having a carbon functional group as R^1 is a novel compound and is useful as an intermediate for preparing the compound of the formula (I).

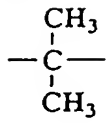
Examples of the compound of the present invention are illustrated as compounds of the formulas (I-1) and (I-2)

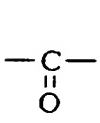
in Tables 1 to 10. Also, the above described salts derived by reacting basic nitrogen at the 3-position of the thiazolidine ring by means of a well known method are also the compounds of the present invention.

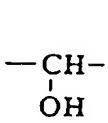
In the Tables, Me is a methyl group; Et is an ethyl group; Pr is a propyl group; Bu is a butyl group; Pen is a pentyl group; Hex is a hexyl group; Hep is a heptyl group; Ph is a phenyl group; n means "normal"; i means "iso"; s means "secondary"; t means "tertiary"; and c means "cyclo". Also, Q1 to Q317 and J1 to J42 represent the following substituents.

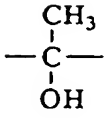
J1

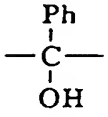
J2 

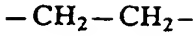
J3 

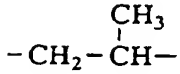
J4 

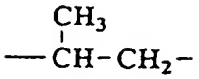
J5 

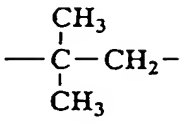
J6 

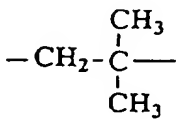
J7 

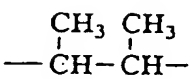
J8 

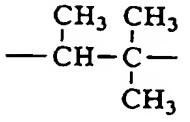
J9 

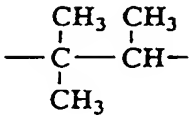
J10 

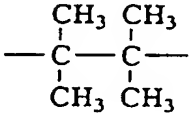
J11 

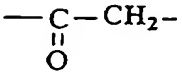
J12 

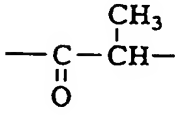
J13 

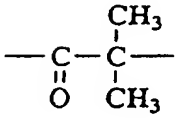
J14 

J15 

J16 

J17 

J18 

J19 

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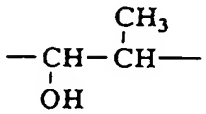
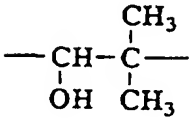
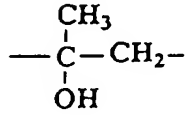
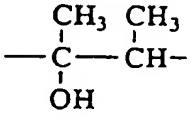
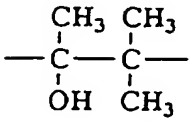
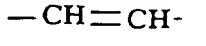
J21 

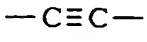
J22 

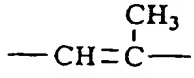
J23 

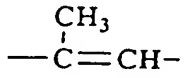
J24 

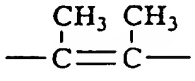
J25 

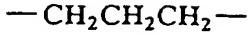
J26 

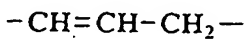
J27 

J28 

J29 

J30 

J31 

J32 

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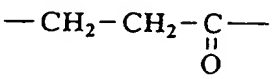
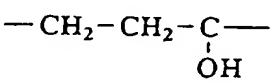
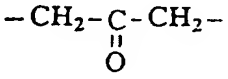
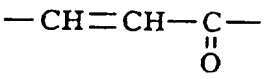
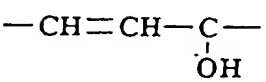
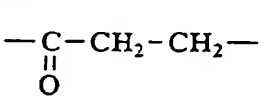
J34 

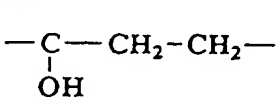
J35 

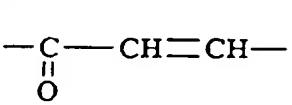
J36 

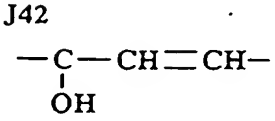
J37 

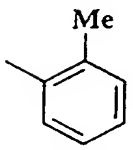
J38 

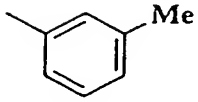
J39 

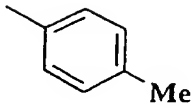
J40 

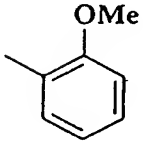
J41 

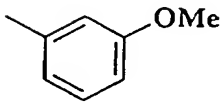
J42 

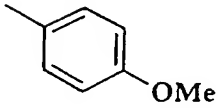
Q1 

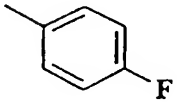
Q2 

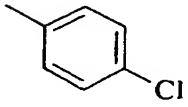
Q3 

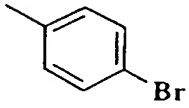
Q4 

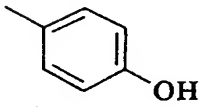
Q5 

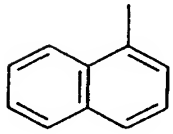
Q6 

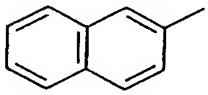
Q7 

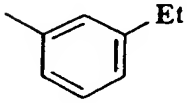
Q8 

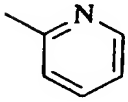
Q9 

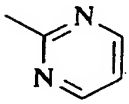
Q10 

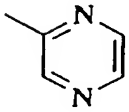
Q11 

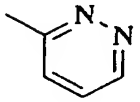
Q12 

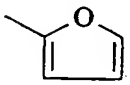
Q13 

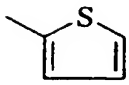
Q14 

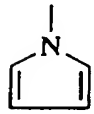
Q15 

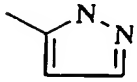
Q16 

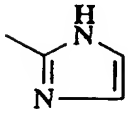
Q17 

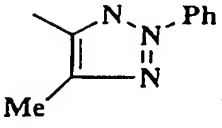
Q18 

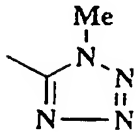
Q19 

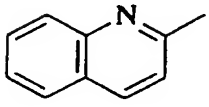
Q20 

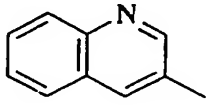
Q21 

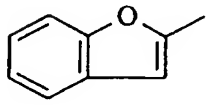
Q22 

Q23 

Q24 

Q25 

Q26 

Q 27 

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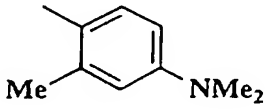

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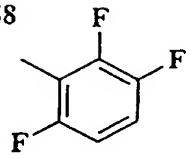

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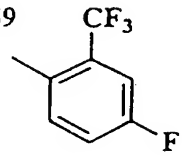

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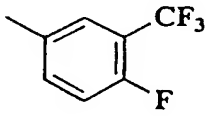

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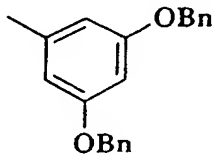

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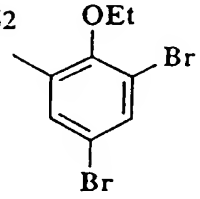

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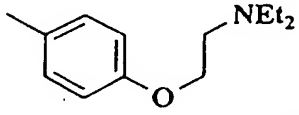

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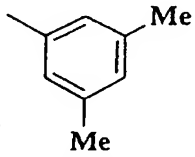

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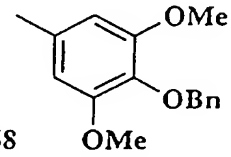

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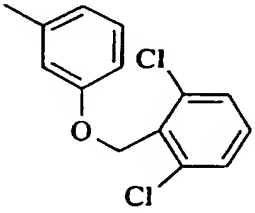

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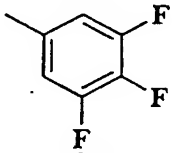

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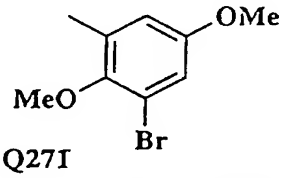

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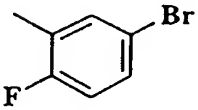

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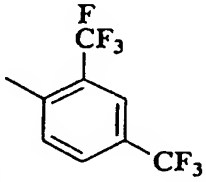

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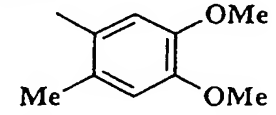

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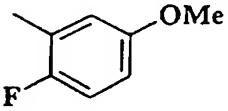

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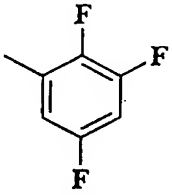

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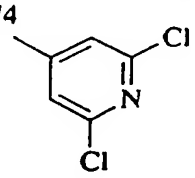

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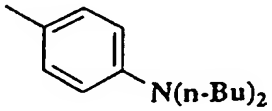

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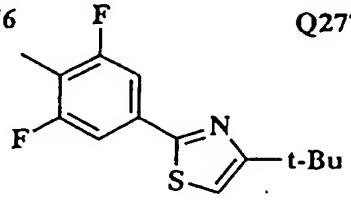

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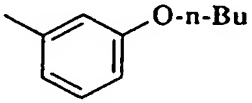

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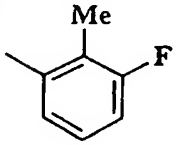

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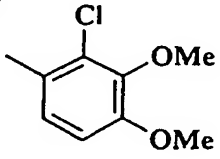

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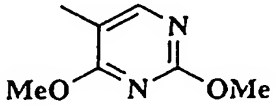

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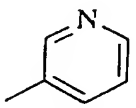

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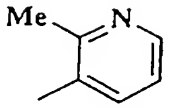

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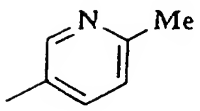

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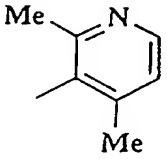

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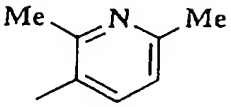

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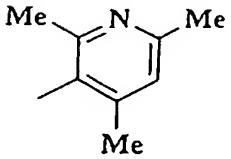

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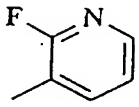

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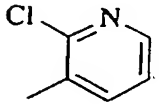

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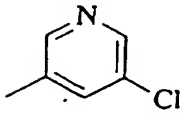

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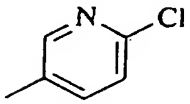

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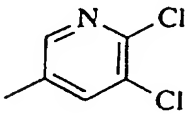

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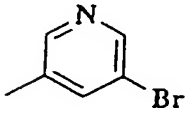

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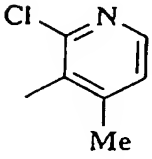

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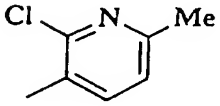

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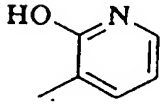

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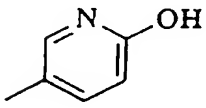

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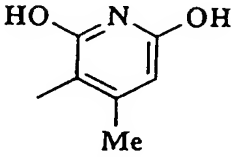

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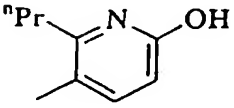

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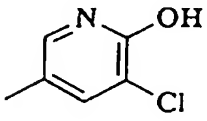

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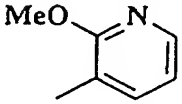

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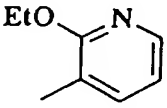

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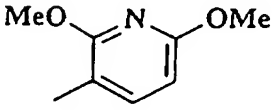

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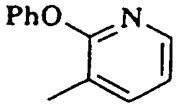

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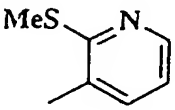

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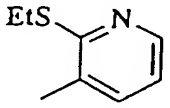

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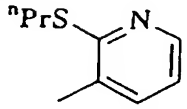

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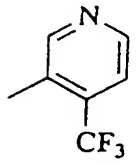

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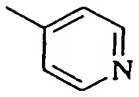

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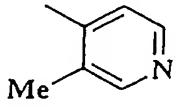

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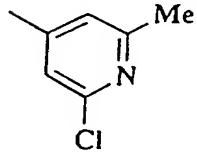

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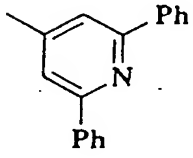

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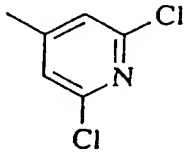

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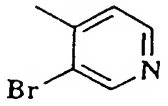

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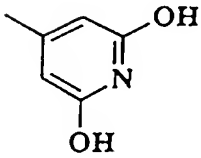

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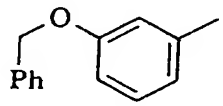

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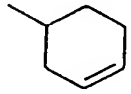

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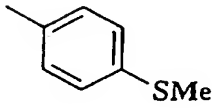

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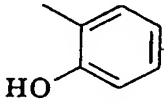

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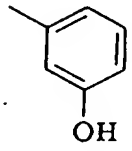

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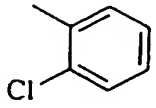

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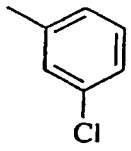

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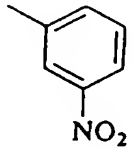

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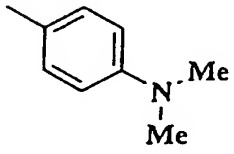

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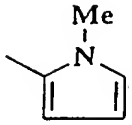

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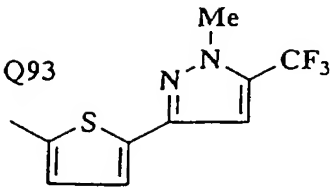

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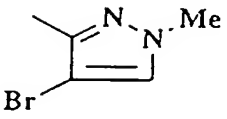

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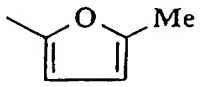

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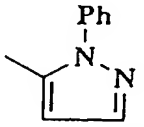

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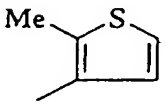

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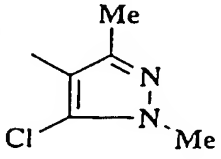

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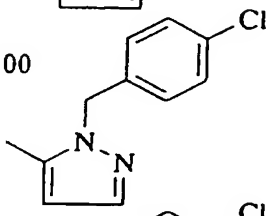

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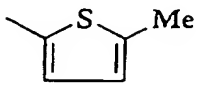

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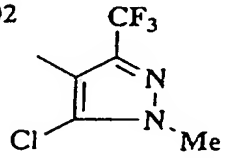

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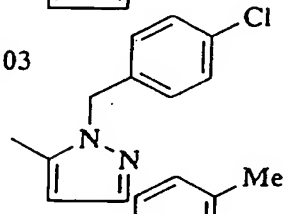

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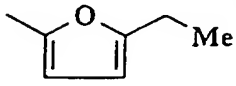

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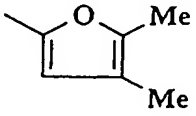

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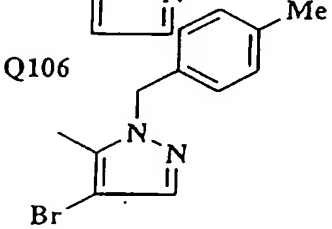

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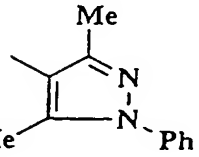

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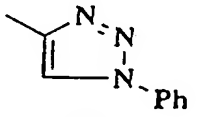

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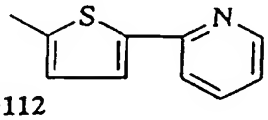

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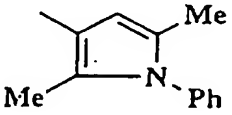

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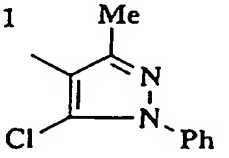

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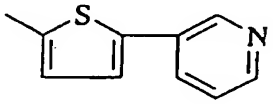

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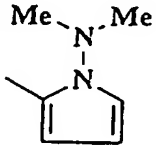

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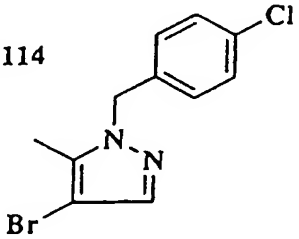

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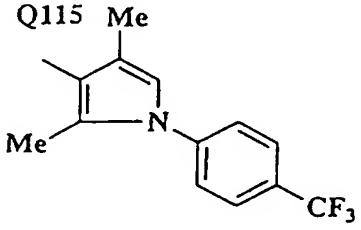

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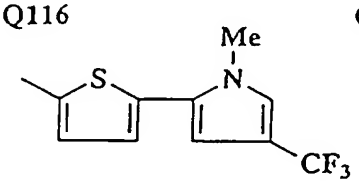

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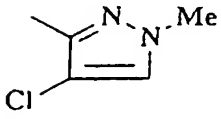

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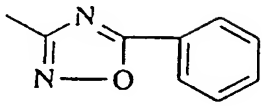

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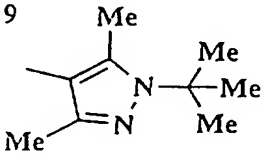

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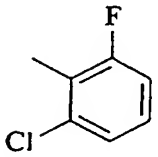

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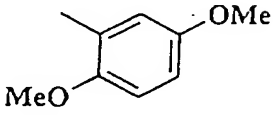

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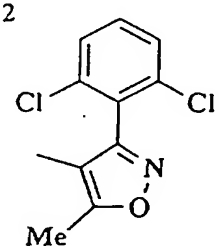

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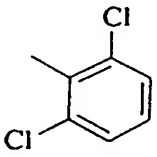

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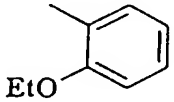

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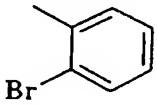

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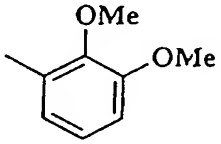

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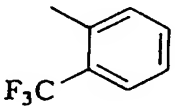

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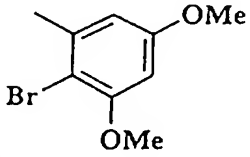

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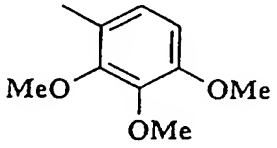

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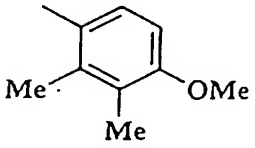

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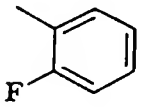

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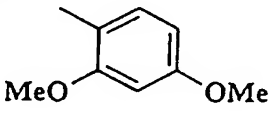

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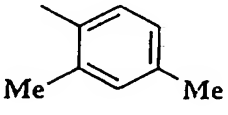

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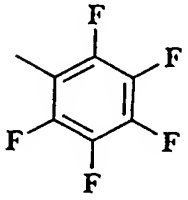

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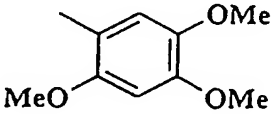

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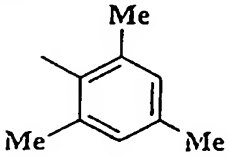

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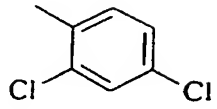

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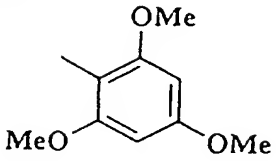

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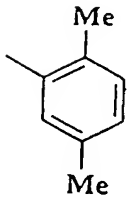

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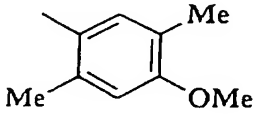

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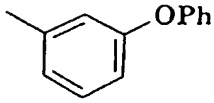

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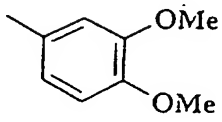

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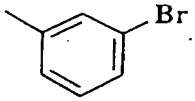

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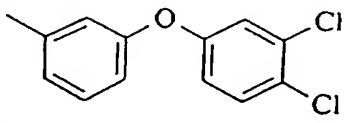

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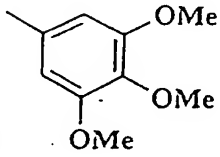

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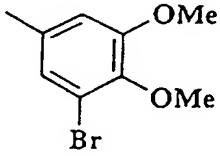

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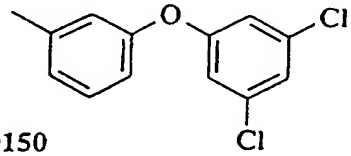

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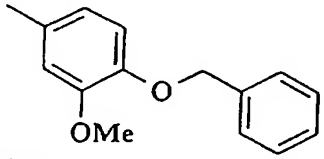

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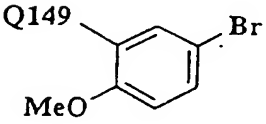

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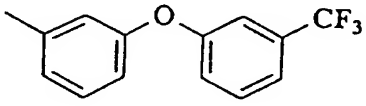

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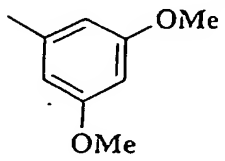

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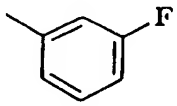

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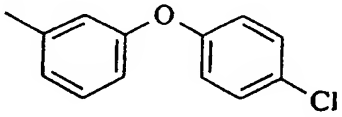

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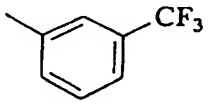

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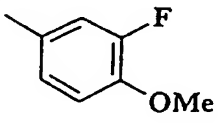

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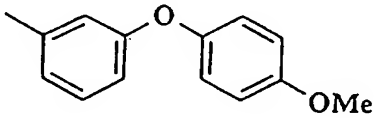

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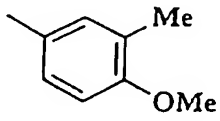

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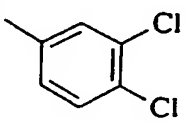

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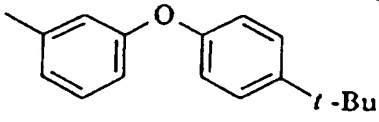

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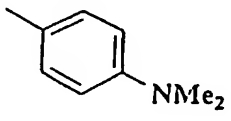

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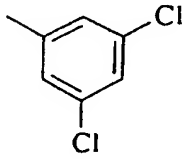

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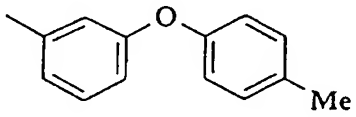

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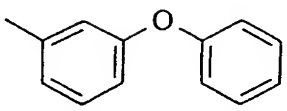

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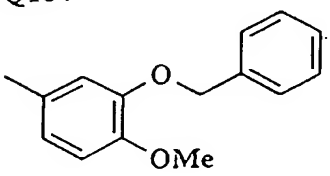

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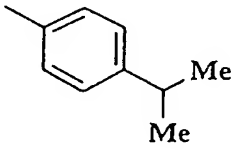

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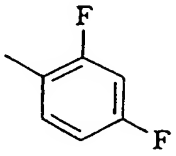

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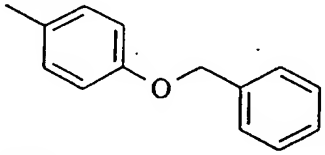

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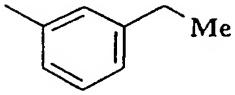

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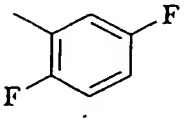

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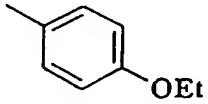

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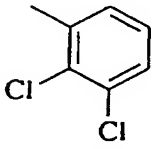

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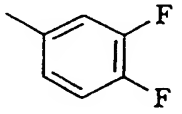

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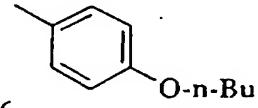

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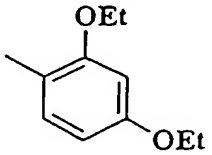

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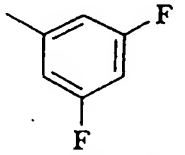

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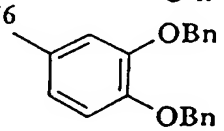

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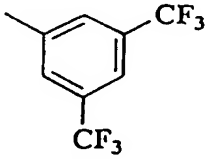

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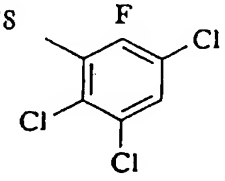

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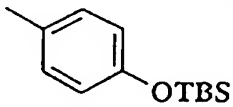

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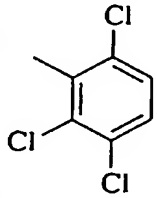

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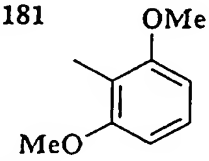

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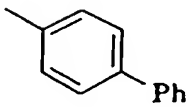

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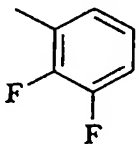

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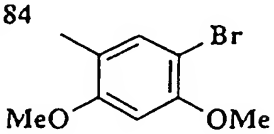

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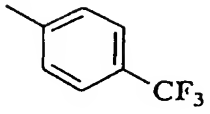

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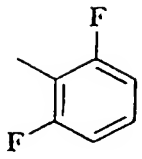

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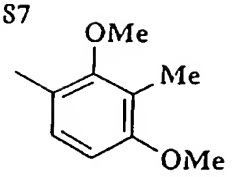

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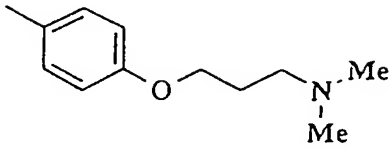

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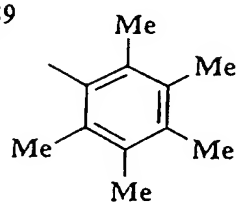

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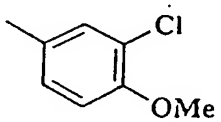

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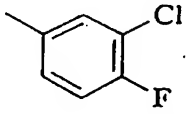

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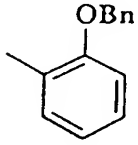

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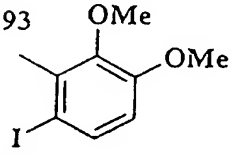

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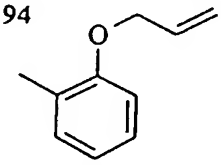

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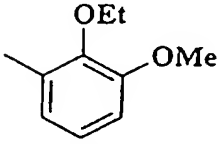

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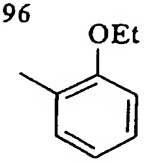

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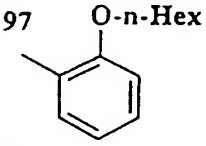

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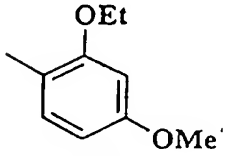

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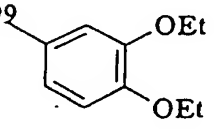

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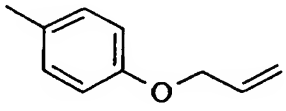

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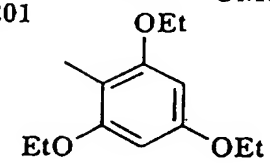

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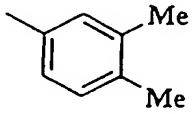

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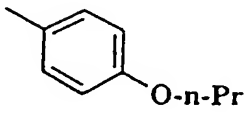

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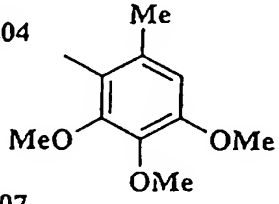

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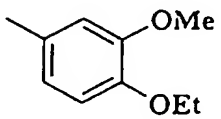

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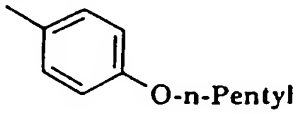

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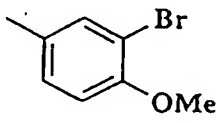

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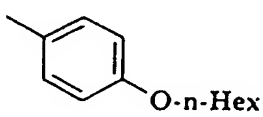

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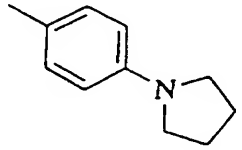

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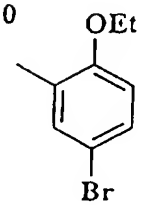

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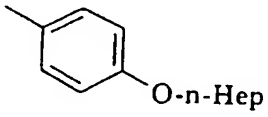

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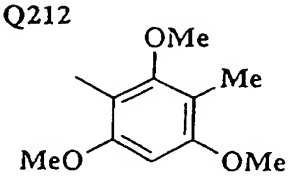

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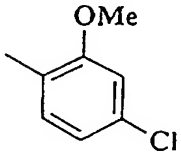

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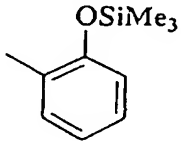

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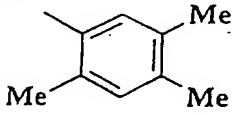

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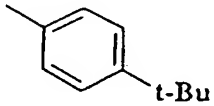

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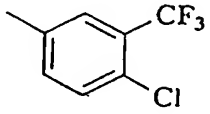

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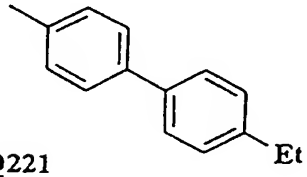

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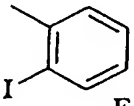

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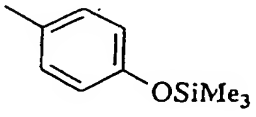

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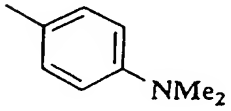

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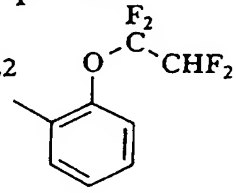

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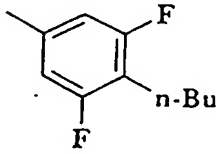

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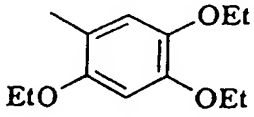

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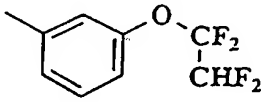

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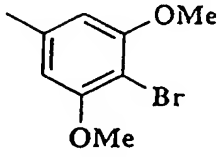

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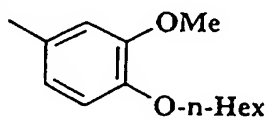

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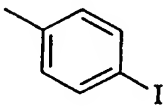

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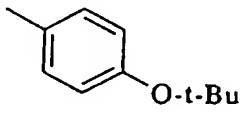

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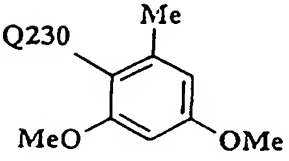

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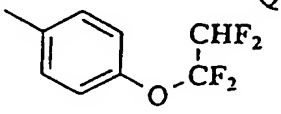

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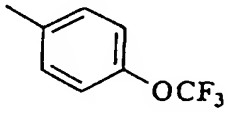

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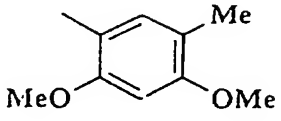

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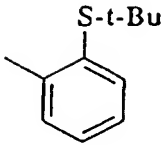

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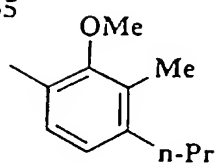

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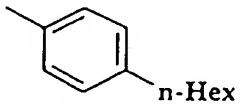

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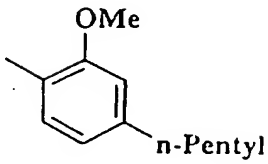

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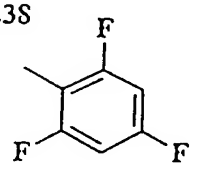

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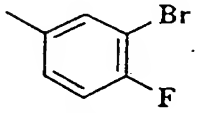

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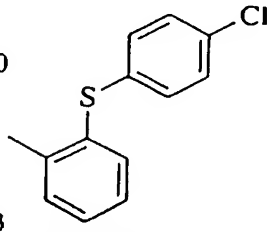

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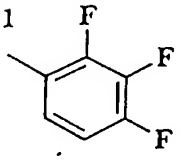

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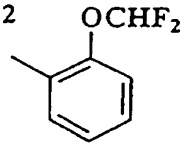

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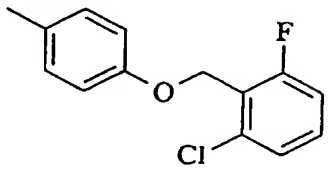

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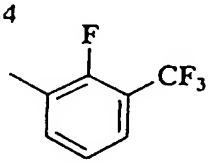

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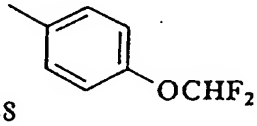

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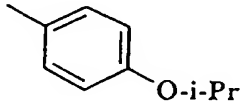

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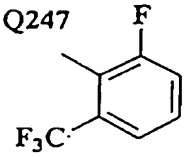

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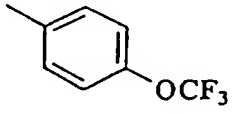

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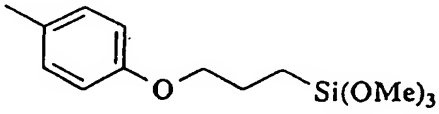

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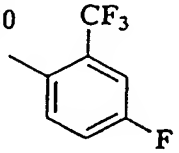

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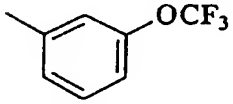

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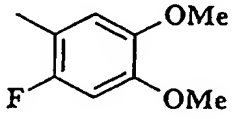

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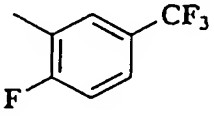

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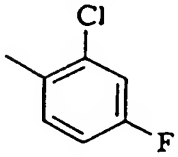

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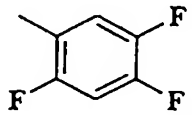

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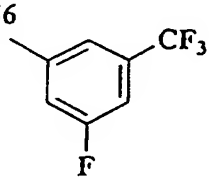

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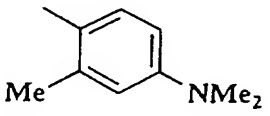

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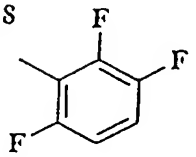

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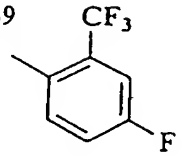

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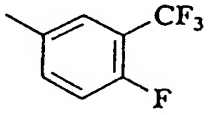

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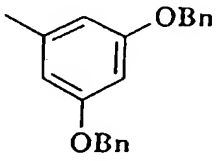

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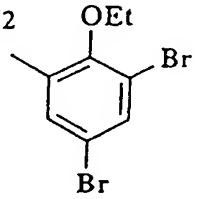

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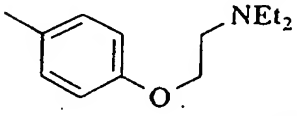

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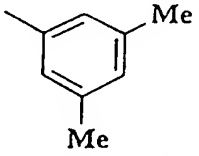

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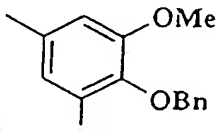

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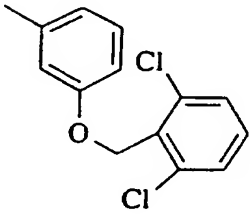

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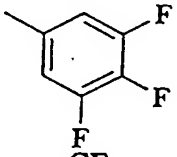

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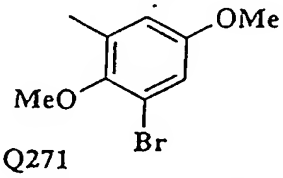

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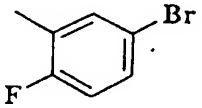

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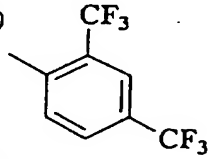

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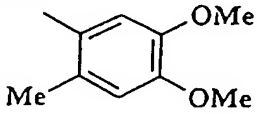

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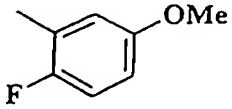

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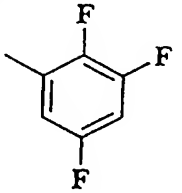

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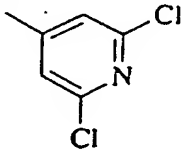

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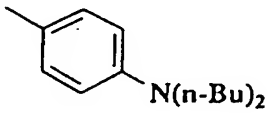

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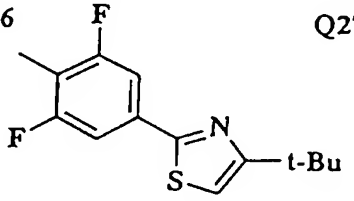

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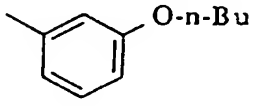

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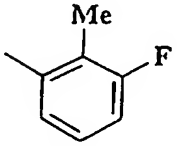

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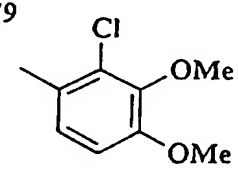

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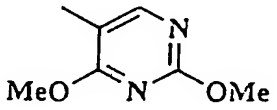

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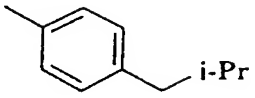

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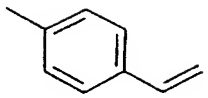

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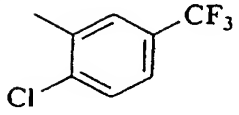

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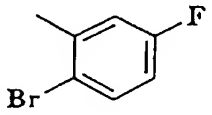

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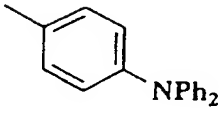

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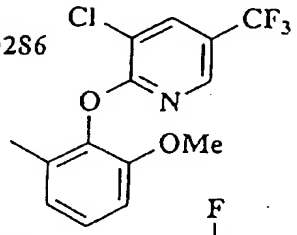

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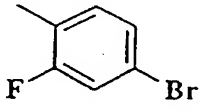

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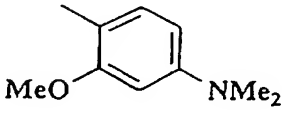

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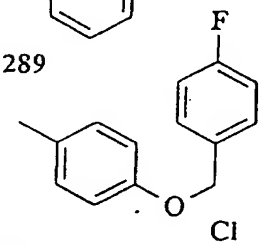

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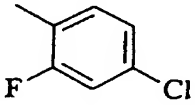

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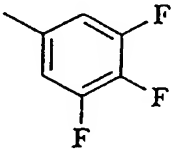

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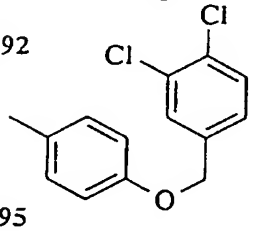

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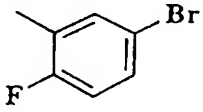

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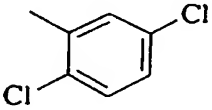

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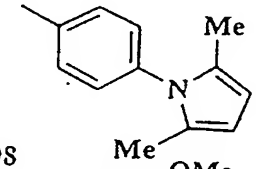

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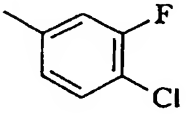

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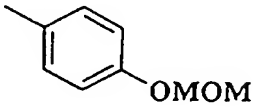

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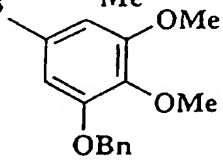

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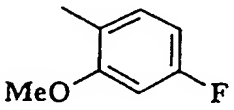

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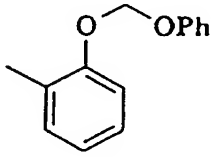

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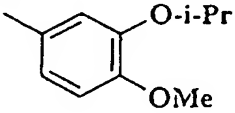

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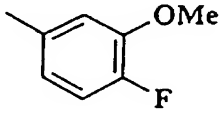

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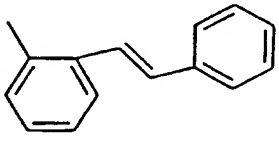

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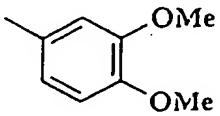
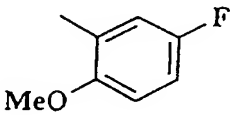
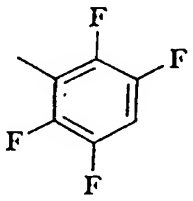


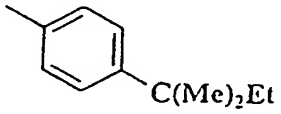
Q305



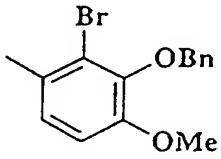
Q306



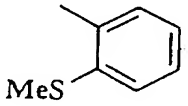
Q307



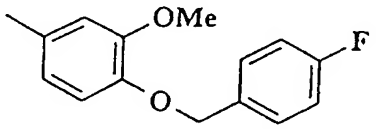
Q308



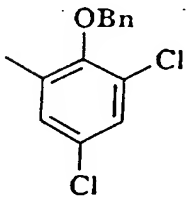
Q309



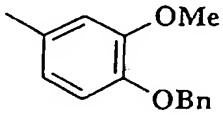
Q310



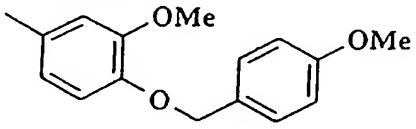
Q311



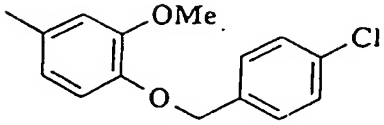
Q312



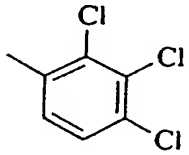
Q313



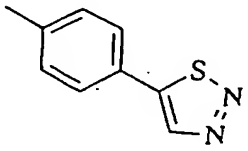
Q314



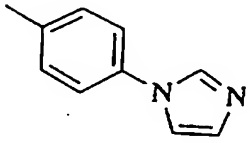
Q315

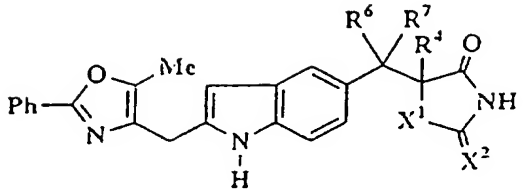


Q316



Q317

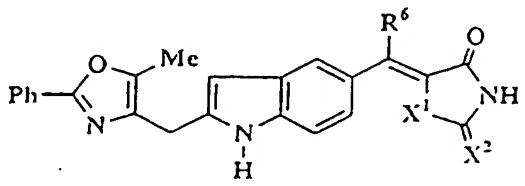




In the above formula, X^1, X^2, R^4, R^6 and R^7 are selected from the following Table 1.

Table 1

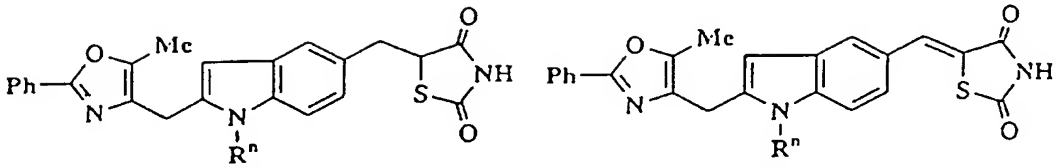
X^1	X^2	R^4	R^6	R^7
S	O	H	H	H
S	S	H	H	H
O	S	H	H	H
O	O	H	H	H
S	O	Me	H	H
S	S	Me	H	H
O	S	Me	H	H
O	O	Me	H	H
S	O	H	H	Me
S	S	H	H	Me
O	S	H	H	Me
O	O	H	H	Me
S	O	Me	H	Me
S	S	Me	H	Me
O	S	Me	H	Me
O	O	Me	H	Me



In the above formula, X^1, X^2 and R^6 are selected from the following Table 2.

Table 2

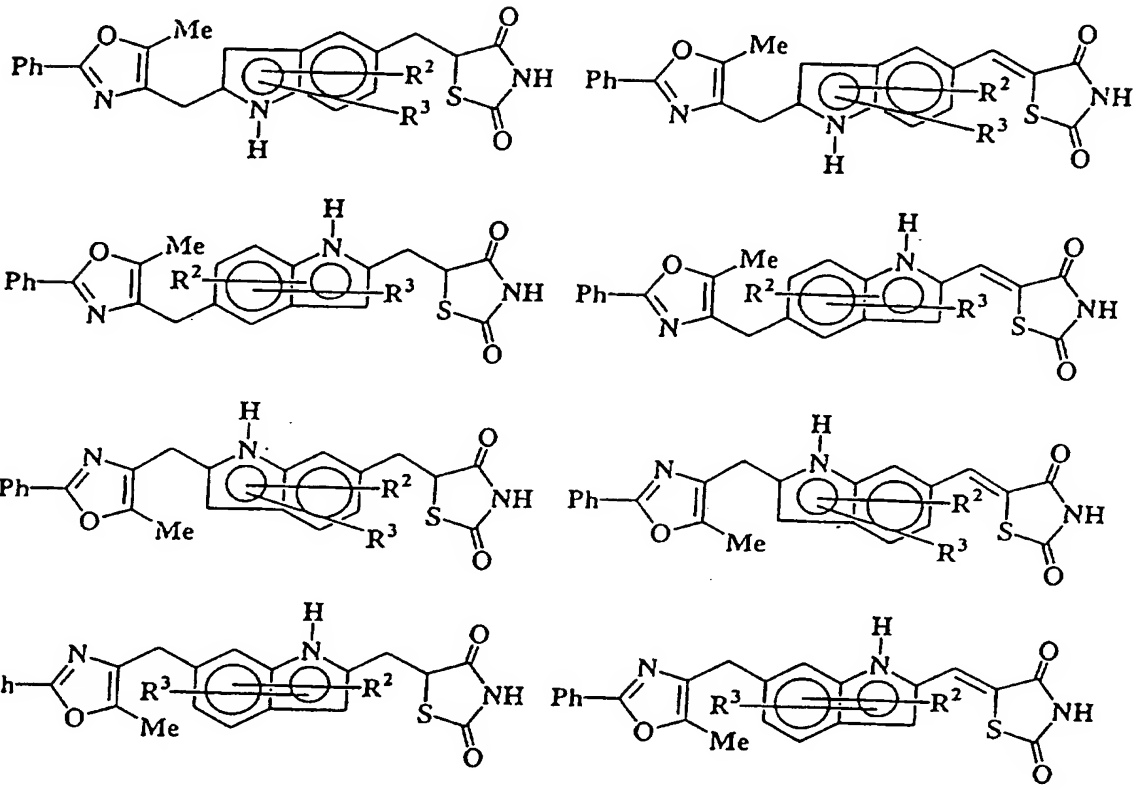
X^1	X^2	R^6
S	O	H
S	S	H
O	S	H
O	O	H
S	O	Me
S	S	Me
O	S	Me
O	O	Me



In the above formula, R^n is selected from the following Table 3.

Table 3

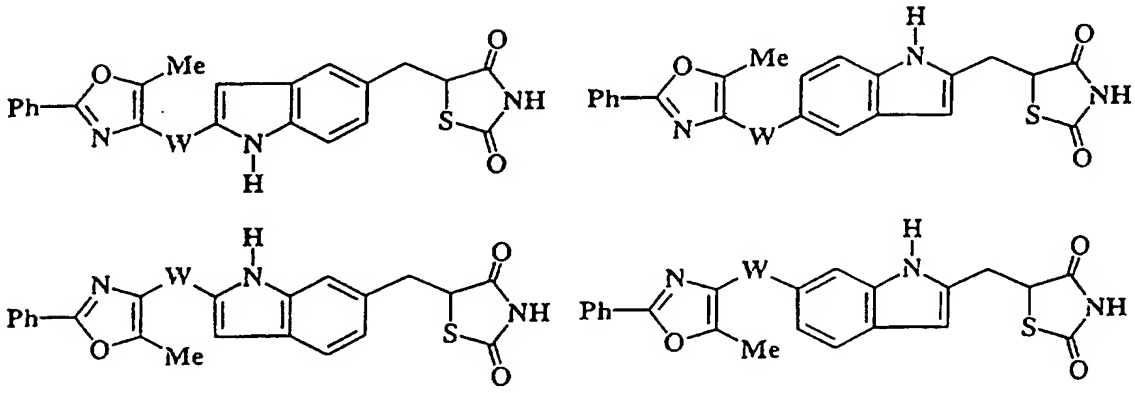
R^n	R^n
H	benzoyl
Me	methoxycarbonyl
^{n}Bu	benzyloxycarbonyl
^{n}Hex	methylcarbamoyl
^{c}Pr	phenylcarbamoyl
^{c}Hex	methoxy
methoxymethyl	n-butoxy
benzyloxymethyl	n-hexyloxy
dimethoxyaminomethyl	methoxymethyloxy
acetamidemethyl	triisopropylsilyl
methylthiomethyl	t-butyldiphenylsilyl
carboxyl	methanesulfonyl
formyl	benzenesulfonyl
acetyl	



In the above formula, R^2 and R^3 are selected from the following Table 4.

Table 4

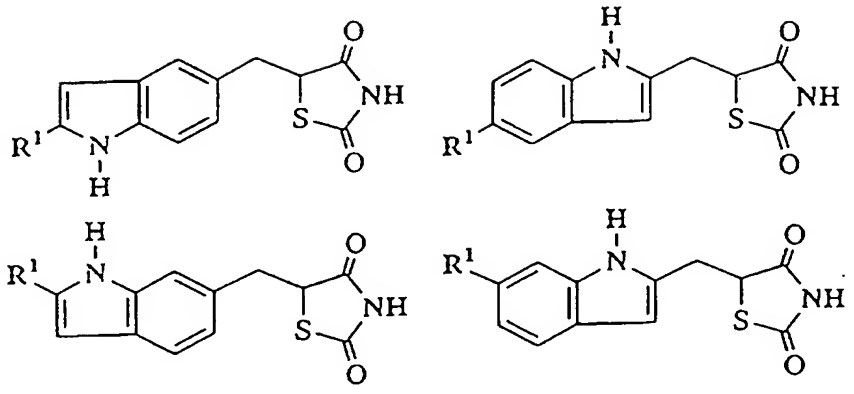
R^2	R^3
3-OH	H
4-OH	H
6-OH	H
7-OH	H
3-Me	H
3-MeO	H
3-$PhCH_2O$	H
3-Ph	H
3-Cl	H



In the above formula, W is selected from the following Table 5.

Table 5

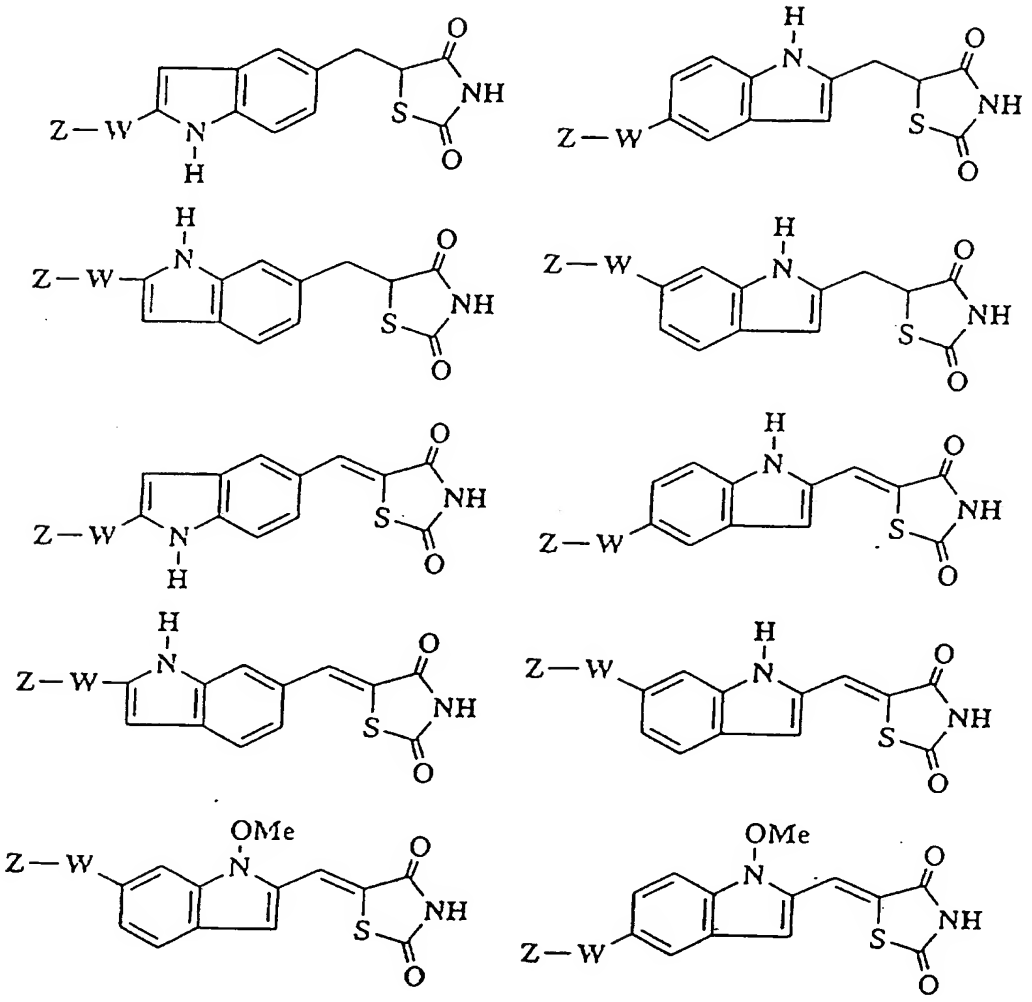
W	W	W	W
J1	J12	J23	J34
J2	J13	J24	J35
J3	J14	J25	J36
J4	J15	J26	J37
J5	J16	J27	J38
J6	J17	J28	J39
J7	J18	J29	J40
J8	J19	J30	J41
J9	J20	J31	J42
J10	J21	J32	
J11	J22	J33	



In the above formula, R^1 is selected from the following Table 6.

Table 6

R^1
n-hexyl
1-hexenyl
1-hexynyl
n-hexyloxy
2-hexenyloxy
n-hexylthio
n-hexylamino
N-methyl-N-n-hexylamino


Z—W
N
H
O
NH
S
OMe

In the above formula, Z and W are selected from the following Tables 7 to 22.

Table 7

Z	W	Z	W	Z	W	Z	W
Q1	J1	Q21	J1	Q41	J1	Q61	J1
Q2	J1	Q22	J1	Q42	J1	Q62	J1
Q3	J1	Q23	J1	Q43	J1	Q63	J1
Q4	J1	Q24	J1	Q44	J1	Q64	J1
Q5	J1	Q25	J1	Q45	J1	Q65	J1
Q6	J1	Q26	J1	Q46	J1	Q66	J1
Q7	J1	Q27	J1	Q47	J1	Q67	J1
Q8	J1	Q28	J1	Q48	J1	Q68	J1
Q9	J1	Q29	J1	Q49	J1	Q69	J1
Q10	J1	Q30	J1	Q50	J1	Q70	J1
Q11	J1	Q31	J1	Q51	J1	Q71	J1
Q12	J1	Q32	J1	Q52	J1	Q72	J1
Q13	J1	Q33	J1	Q53	J1	Q73	J1
Q14	J1	Q34	J1	Q54	J1	Q74	J1
Q15	J1	Q35	J1	Q55	J1	Q75	J1
Q16	J1	Q36	J1	Q56	J1	Q76	J1
Q17	J1	Q37	J1	Q57	J1	Q77	J1
Q18	J1	Q38	J1	Q58	J1	Q78	J1
Q19	J1	Q39	J1	Q59	J1	Q79	J1
Q20	J1	Q40	J1	Q60	J1	Q80	J1

Table 8

Z	W	Z	W	Z	W	Z	W
Q81	J1	Q101	J1	Q121	J1	Q141	J1
Q82	J1	Q102	J1	Q122	J1	Q142	J1
Q83	J1	Q103	J1	Q123	J1	Q143	J1
Q84	J1	Q104	J1	Q124	J1	Q144	J1
Q85	J1	Q105	J1	Q125	J1	Q145	J1
Q86	J1	Q106	J1	Q126	J1	Q146	J1
Q87	J1	Q107	J1	Q127	J1	Q147	J1
Q88	J1	Q108	J1	Q128	J1	Q148	J1
Q89	J1	Q109	J1	Q129	J1	Q149	J1
Q90	J1	Q110	J1	Q130	J1	Q150	J1
Q91	J1	Q111	J1	Q131	J1	Q151	J1
Q92	J1	Q112	J1	Q132	J1	Q152	J1
Q93	J1	Q113	J1	Q133	J1	Q153	J1
Q94	J1	Q114	J1	Q134	J1	Q154	J1
Q95	J1	Q115	J1	Q135	J1	Q155	J1
Q96	J1	Q116	J1	Q136	J1	Q156	J1
Q97	J1	Q117	J1	Q137	J1	Q157	J1
Q98	J1	Q118	J1	Q138	J1	Q158	J1
Q99	J1	Q119	J1	Q139	J1	Q159	J1
Q100	J1	Q120	J1	Q140	J1	Q160	J1

Table 9

Z	W	Z	W	Z	W	Z	W
Q161	J1	Q181	J1	Q201	J1	Q221	J1
Q162	J1	Q182	J1	Q202	J1	Q222	J1
Q163	J1	Q183	J1	Q203	J1	Q223	J1
Q164	J1	Q184	J1	Q204	J1	Q224	J1
Q165	J1	Q185	J1	Q205	J1	Q225	J1
Q166	J1	Q186	J1	Q206	J1	Q226	J1
Q167	J1	Q187	J1	Q207	J1	Q227	J1
Q168	J1	Q188	J1	Q208	J1	Q228	J1
Q169	J1	Q189	J1	Q209	J1	Q229	J1
Q170	J1	Q190	J1	Q210	J1	Q230	J1
Q171	J1	Q191	J1	Q211	J1	Q231	J1
Q172	J1	Q192	J1	Q212	J1	Q232	J1
Q173	J1	Q193	J1	Q213	J1	Q233	J1
Q174	J1	Q194	J1	Q214	J1	Q234	J1
Q175	J1	Q195	J1	Q215	J1	Q235	J1
Q176	J1	Q196	J1	Q216	J1	Q236	J1
Q177	J1	Q197	J1	Q217	J1	Q237	J1
Q178	J1	Q198	J1	Q218	J1	Q238	J1
Q179	J1	Q199	J1	Q219	J1	Q239	J1
Q180	J1	Q200	J1	Q220	J1	Q240	J1

Table 10

Z	W	Z	W	Z	W	Z	W
Q241	J1	Q261	J1	Q281	J1	Q301	J1
Q242	J1	Q262	J1	Q282	J1	Q302	J1
Q243	J1	Q263	J1	Q283	J1	Q303	J1
Q244	J1	Q264	J1	Q284	J1	Q304	J1
Q245	J1	Q265	J1	Q285	J1	Q305	J1
Q246	J1	Q266	J1	Q286	J1	Q306	J1
Q247	J1	Q267	J1	Q287	J1	Q307	J1
Q248	J1	Q268	J1	Q288	J1	Q308	J1
Q249	J1	Q269	J1	Q289	J1	Q309	J1
Q250	J1	Q270	J1	Q290	J1	Q310	J1
Q251	J1	Q271	J1	Q291	J1	Q311	J1
Q252	J1	Q272	J1	Q292	J1	Q312	J1
Q253	J1	Q273	J1	Q293	J1	Q313	J1
Q254	J1	Q274	J1	Q294	J1	Q314	J1
Q255	J1	Q275	J1	Q295	J1	Q315	J1
Q256	J1	Q276	J1	Q296	J1	Q316	J1
Q257	J1	Q277	J1	Q297	J1	Q317	J1
Q258	J1	Q278	J1	Q298	J1		
Q259	J1	Q279	J1	Q299	J1		
Q260	J1	Q280	J1	Q300	J1		

Table 11

Z	W	Z	W	Z	W	Z	W
Q1	J2	Q21	J2	Q41	J2	Q61	J2
Q2	J2	Q22	J2	Q42	J2	Q62	J2
Q3	J2	Q23	J2	Q43	J2	Q63	J2
Q4	J2	Q24	J2	Q44	J2	Q64	J2
Q5	J2	Q25	J2	Q45	J2	Q65	J2
Q6	J2	Q26	J2	Q46	J2	Q66	J2
Q7	J2	Q27	J2	Q47	J2	Q67	J2
Q8	J2	Q28	J2	Q48	J2	Q68	J2
Q9	J2	Q29	J2	Q49	J2	Q69	J2
Q10	J2	Q30	J2	Q50	J2	Q70	J2
Q11	J2	Q31	J2	Q51	J2	Q71	J2
Q12	J2	Q32	J2	Q52	J2	Q72	J2
Q13	J2	Q33	J2	Q53	J2	Q73	J2
Q14	J2	Q34	J2	Q54	J2	Q74	J2
Q15	J2	Q35	J2	Q55	J2	Q75	J2
Q16	J2	Q36	J2	Q56	J2	Q76	J2
Q17	J2	Q37	J2	Q57	J2	Q77	J2
Q18	J2	Q38	J2	Q58	J2	Q78	J2
Q19	J2	Q39	J2	Q59	J2	Q79	J2
Q20	J2	Q40	J2	Q60	J2	Q80	J2

Table 12

Z	W	Z	W	Z	W	Z	W
Q81	J2	Q101	J2	Q121	J2	Q141	J2
Q82	J2	Q102	J2	Q122	J2	Q142	J2
Q83	J2	Q103	J2	Q123	J2	Q143	J2
Q84	J2	Q104	J2	Q124	J2	Q144	J2
Q85	J2	Q105	J2	Q125	J2	Q145	J2
Q86	J2	Q106	J2	Q126	J2	Q146	J2
Q87	J2	Q107	J2	Q127	J2	Q147	J2
Q88	J2	Q108	J2	Q128	J2	Q148	J2
Q89	J2	Q109	J2	Q129	J2	Q149	J2
Q90	J2	Q110	J2	Q130	J2	Q150	J2
Q91	J2	Q111	J2	Q131	J2	Q151	J2
Q92	J2	Q112	J2	Q132	J2	Q152	J2
Q93	J2	Q113	J2	Q133	J2	Q153	J2
Q94	J2	Q114	J2	Q134	J2	Q154	J2
Q95	J2	Q115	J2	Q135	J2	Q155	J2
Q96	J2	Q116	J2	Q136	J2	Q156	J2
Q97	J2	Q117	J2	Q137	J2	Q157	J2
Q98	J2	Q118	J2	Q138	J2	Q158	J2
Q99	J2	Q119	J2	Q139	J2	Q159	J2
Q100	J2	Q120	J2	Q140	J2	Q160	J2

Table 13

Z	W	Z	W	Z	W	Z	W
Q161	J2	Q181	J2	Q201	J2	Q221	J2
Q162	J2	Q182	J2	Q202	J2	Q222	J2
Q163	J2	Q183	J2	Q203	J2	Q223	J2
Q164	J2	Q184	J2	Q204	J2	Q224	J2
Q165	J2	Q185	J2	Q205	J2	Q225	J2
Q166	J2	Q186	J2	Q206	J2	Q226	J2
Q167	J2	Q187	J2	Q207	J2	Q227	J2
Q168	J2	Q188	J2	Q208	J2	Q228	J2
Q169	J2	Q189	J2	Q209	J2	Q229	J2
Q170	J2	Q190	J2	Q210	J2	Q230	J2
Q171	J2	Q191	J2	Q211	J2	Q231	J2
Q172	J2	Q192	J2	Q212	J2	Q232	J2
Q173	J2	Q193	J2	Q213	J2	Q233	J2
Q174	J2	Q194	J2	Q214	J2	Q234	J2
Q175	J2	Q195	J2	Q215	J2	Q235	J2
Q176	J2	Q196	J2	Q216	J2	Q236	J2
Q177	J2	Q197	J2	Q217	J2	Q237	J2
Q178	J2	Q198	J2	Q218	J2	Q238	J2
Q179	J2	Q199	J2	Q219	J2	Q239	J2
Q180	J2	Q200	J2	Q220	J2	Q240	J2

Table 14

Z	W	Z	W	Z	W	Z	W
Q241	J2	Q261	J2	Q281	J2	Q301	J2
Q242	J2	Q262	J2	Q282	J2	Q302	J2
Q243	J2	Q263	J2	Q283	J2	Q303	J2
Q244	J2	Q264	J2	Q284	J2	Q304	J2
Q245	J2	Q265	J2	Q285	J2	Q305	J2
Q246	J2	Q266	J2	Q286	J2	Q306	J2
Q247	J2	Q267	J2	Q287	J2	Q307	J2
Q248	J2	Q268	J2	Q288	J2	Q308	J2
Q249	J2	Q269	J2	Q289	J2	Q309	J2
Q250	J2	Q270	J2	Q290	J2	Q310	J2
Q251	J2	Q271	J2	Q291	J2	Q311	J2
Q252	J2	Q272	J2	Q292	J2	Q312	J2
Q253	J2	Q273	J2	Q293	J2	Q313	J2
Q254	J2	Q274	J2	Q294	J2	Q314	J2
Q255	J2	Q275	J2	Q295	J2	Q315	J2
Q256	J2	Q276	J2	Q296	J2	Q316	J2
Q257	J2	Q277	J2	Q297	J2	Q317	J2
Q258	J2	Q278	J2	Q298	J2		
Q259	J2	Q279	J2	Q299	J2		
Q260	J2	Q280	J2	Q300	J2		

Table 15

Z	W	Z	W	Z	W	Z	W
Q1	J4	Q21	J4	Q41	J4	Q61	J4
Q2	J4	Q22	J4	Q42	J4	Q62	J4
Q3	J4	Q23	J4	Q43	J4	Q63	J4
Q4	J4	Q24	J4	Q44	J4	Q64	J4
Q5	J4	Q25	J4	Q45	J4	Q65	J4
Q6	J4	Q26	J4	Q46	J4	Q66	J4
Q7	J4	Q27	J4	Q47	J4	Q67	J4
Q8	J4	Q28	J4	Q48	J4	Q68	J4
Q9	J4	Q29	J4	Q49	J4	Q69	J4
Q10	J4	Q30	J4	Q50	J4	Q70	J4
Q11	J4	Q31	J4	Q51	J4	Q71	J4
Q12	J4	Q32	J4	Q52	J4	Q72	J4
Q13	J4	Q33	J4	Q53	J4	Q73	J4
Q14	J4	Q34	J4	Q54	J4	Q74	J4
Q15	J4	Q35	J4	Q55	J4	Q75	J4
Q16	J4	Q36	J4	Q56	J4	Q76	J4
Q17	J4	Q37	J4	Q57	J4	Q77	J4
Q18	J4	Q38	J4	Q58	J4	Q78	J4
Q19	J4	Q39	J4	Q59	J4	Q79	J4
Q20	J4	Q40	J4	Q60	J4	Q80	J4

Table 16

Z	W	Z	W	Z	W	Z	W
Q81	J4	Q101	J4	Q121	J4	Q141	J4
Q82	J4	Q102	J4	Q122	J4	Q142	J4
Q83	J4	Q103	J4	Q123	J4	Q143	J4
Q84	J4	Q104	J4	Q124	J4	Q144	J4
Q85	J4	Q105	J4	Q125	J4	Q145	J4
Q86	J4	Q106	J4	Q126	J4	Q146	J4
Q87	J4	Q107	J4	Q127	J4	Q147	J4
Q88	J4	Q108	J4	Q128	J4	Q148	J4
Q89	J4	Q109	J4	Q129	J4	Q149	J4
Q90	J4	Q110	J4	Q130	J4	Q150	J4
Q91	J4	Q111	J4	Q131	J4	Q151	J4
Q92	J4	Q112	J4	Q132	J4	Q152	J4
Q93	J4	Q113	J4	Q133	J4	Q153	J4
Q94	J4	Q114	J4	Q134	J4	Q154	J4
Q95	J4	Q115	J4	Q135	J4	Q155	J4
Q96	J4	Q116	J4	Q136	J4	Q156	J4
Q97	J4	Q117	J4	Q137	J4	Q157	J4
Q98	J4	Q118	J4	Q138	J4	Q158	J4
Q99	J4	Q119	J4	Q139	J4	Q159	J4
Q100	J4	Q120	J4	Q140	J4	Q160	J4

Table 17

Z	W	Z	W	Z	W	Z	W
Q161	J4	Q181	J4	Q201	J4	Q221	J4
Q162	J4	Q182	J4	Q202	J4	Q222	J4
Q163	J4	Q183	J4	Q203	J4	Q223	J4
Q164	J4	Q184	J4	Q204	J4	Q224	J4
Q165	J4	Q185	J4	Q205	J4	Q225	J4
Q166	J4	Q186	J4	Q206	J4	Q226	J4
Q167	J4	Q187	J4	Q207	J4	Q227	J4
Q168	J4	Q188	J4	Q208	J4	Q228	J4
Q169	J4	Q189	J4	Q209	J4	Q229	J4
Q170	J4	Q190	J4	Q210	J4	Q230	J4
Q171	J4	Q191	J4	Q211	J4	Q231	J4
Q172	J4	Q192	J4	Q212	J4	Q232	J4
Q173	J4	Q193	J4	Q213	J4	Q233	J4
Q174	J4	Q194	J4	Q214	J4	Q234	J4
Q175	J4	Q195	J4	Q215	J4	Q235	J4
Q176	J4	Q196	J4	Q216	J4	Q236	J4
Q177	J4	Q197	J4	Q217	J4	Q237	J4
Q178	J4	Q198	J4	Q218	J4	Q238	J4
Q179	J4	Q199	J4	Q219	J4	Q239	J4
Q180	J4	Q200	J4	Q220	J4	Q240	J4

Table 18

Z	W	Z	W	Z	W	Z	W
Q241	J4	Q261	J4	Q281	J4	Q301	J4
Q242	J4	Q262	J4	Q282	J4	Q302	J4
Q243	J4	Q263	J4	Q283	J4	Q303	J4
Q244	J4	Q264	J4	Q284	J4	Q304	J4
Q245	J4	Q265	J4	Q285	J4	Q305	J4
Q246	J4	Q266	J4	Q286	J4	Q306	J4
Q247	J4	Q267	J4	Q287	J4	Q307	J4
Q248	J4	Q268	J4	Q288	J4	Q308	J4
Q249	J4	Q269	J4	Q289	J4	Q309	J4
Q250	J4	Q270	J4	Q290	J4	Q310	J4
Q251	J4	Q271	J4	Q291	J4	Q311	J4
Q252	J4	Q272	J4	Q292	J4	Q312	J4
Q253	J4	Q273	J4	Q293	J4	Q313	J4
Q254	J4	Q274	J4	Q294	J4	Q314	J4
Q255	J4	Q275	J4	Q295	J4	Q315	J4
Q256	J4	Q276	J4	Q296	J4	Q316	J4
Q257	J4	Q277	J4	Q297	J4	Q317	J4
Q258	J4	Q278	J4	Q298	J4		
Q259	J4	Q279	J4	Q299	J4		
Q260	J4	Q280	J4	Q300	J4		

Table 19

Z	W	Z	W	Z	W	Z	W
Q1	J5	Q21	J5	Q41	J5	Q61	J5
Q2	J5	Q22	J5	Q42	J5	Q62	J5
Q3	J5	Q23	J5	Q43	J5	Q63	J5
Q4	J5	Q24	J5	Q44	J5	Q64	J5
Q5	J5	Q25	J5	Q45	J5	Q65	J5
Q6	J5	Q26	J5	Q46	J5	Q66	J5
Q7	J5	Q27	J5	Q47	J5	Q67	J5
Q8	J5	Q28	J5	Q48	J5	Q68	J5
Q9	J5	Q29	J5	Q49	J5	Q69	J5
Q10	J5	Q30	J5	Q50	J5	Q70	J5
Q11	J5	Q31	J5	Q51	J5	Q71	J5
Q12	J5	Q32	J5	Q52	J5	Q72	J5
Q13	J5	Q33	J5	Q53	J5	Q73	J5
Q14	J5	Q34	J5	Q54	J5	Q74	J5
Q15	J5	Q35	J5	Q55	J5	Q75	J5
Q16	J5	Q36	J5	Q56	J5	Q76	J5
Q17	J5	Q37	J5	Q57	J5	Q77	J5
Q18	J5	Q38	J5	Q58	J5	Q78	J5
Q19	J5	Q39	J5	Q59	J5	Q79	J5
Q20	J5	Q40	J5	Q60	J5	Q80	J5

Table 20

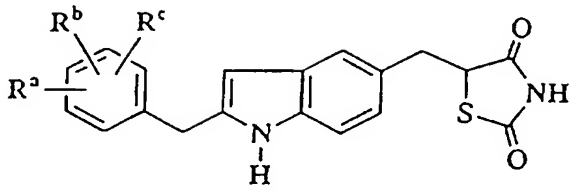
Z	W	Z	W	Z	W	Z	W
Q81	J5	Q101	J5	Q121	J5	Q141	J5
Q82	J5	Q102	J5	Q122	J5	Q142	J5
Q83	J5	Q103	J5	Q123	J5	Q143	J5
Q84	J5	Q104	J5	Q124	J5	Q144	J5
Q85	J5	Q105	J5	Q125	J5	Q145	J5
Q86	J5	Q106	J5	Q126	J5	Q146	J5
Q87	J5	Q107	J5	Q127	J5	Q147	J5
Q88	J5	Q108	J5	Q128	J5	Q148	J5
Q89	J5	Q109	J5	Q129	J5	Q149	J5
Q90	J5	Q110	J5	Q130	J5	Q150	J5
Q91	J5	Q111	J5	Q131	J5	Q151	J5
Q92	J5	Q112	J5	Q132	J5	Q152	J5
Q93	J5	Q113	J5	Q133	J5	Q153	J5
Q94	J5	Q114	J5	Q134	J5	Q154	J5
Q95	J5	Q115	J5	Q135	J5	Q155	J5
Q96	J5	Q116	J5	Q136	J5	Q156	J5
Q97	J5	Q117	J5	Q137	J5	Q157	J5
Q98	J5	Q118	J5	Q138	J5	Q158	J5
Q99	J5	Q119	J5	Q139	J5	Q159	J5
Q100	J5	Q120	J5	Q140	J5	Q160	J5

Table 21

Z	W	Z	W	Z	W	Z	W
Q161	J5	Q181	J5	Q201	J5	Q221	J5
Q162	J5	Q182	J5	Q202	J5	Q222	J5
Q163	J5	Q183	J5	Q203	J5	Q223	J5
Q164	J5	Q184	J5	Q204	J5	Q224	J5
Q165	J5	Q185	J5	Q205	J5	Q225	J5
Q166	J5	Q186	J5	Q206	J5	Q226	J5
Q167	J5	Q187	J5	Q207	J5	Q227	J5
Q168	J5	Q188	J5	Q208	J5	Q228	J5
Q169	J5	Q189	J5	Q209	J5	Q229	J5
Q170	J5	Q190	J5	Q210	J5	Q230	J5
Q171	J5	Q191	J5	Q211	J5	Q231	J5
Q172	J5	Q192	J5	Q212	J5	Q232	J5
Q173	J5	Q193	J5	Q213	J5	Q233	J5
Q174	J5	Q194	J5	Q214	J5	Q234	J5
Q175	J5	Q195	J5	Q215	J5	Q235	J5
Q176	J5	Q196	J5	Q216	J5	Q236	J5
Q177	J5	Q197	J5	Q217	J5	Q237	J5
Q178	J5	Q198	J5	Q218	J5	Q238	J5
Q179	J5	Q199	J5	Q219	J5	Q239	J5
Q180	J5	Q200	J5	Q220	J5	Q240	J5

Table 22

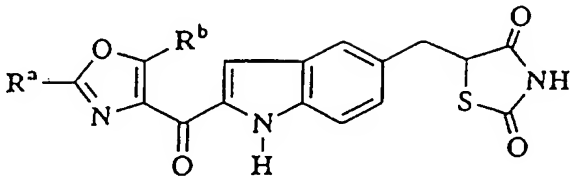
Z	W	Z	W	Z	W	Z	W
Q241	J5	Q261	J5	Q281	J5	Q301	J5
Q242	J5	Q262	J5	Q282	J5	Q302	J5
Q243	J5	Q263	J5	Q283	J5	Q303	J5
Q244	J5	Q264	J5	Q284	J5	Q304	J5
Q245	J5	Q265	J5	Q285	J5	Q305	J5
Q246	J5	Q266	J5	Q286	J5	Q306	J5
Q247	J5	Q267	J5	Q287	J5	Q307	J5
Q248	J5	Q268	J5	Q288	J5	Q308	J5
Q249	J5	Q269	J5	Q289	J5	Q309	J5
Q250	J5	Q270	J5	Q290	J5	Q310	J5
Q251	J5	Q271	J5	Q291	J5	Q311	J5
Q252	J5	Q272	J5	Q292	J5	Q312	J5
Q253	J5	Q273	J5	Q293	J5	Q313	J5
Q254	J5	Q274	J5	Q294	J5	Q314	J5
Q255	J5	Q275	J5	Q295	J5	Q315	J5
Q256	J5	Q276	J5	Q296	J5	Q316	J5
Q257	J5	Q277	J5	Q297	J5	Q317	J5
Q258	J5	Q278	J5	Q298	J5		
Q259	J5	Q279	J5	Q299	J5		
Q260	J5	Q280	J5	Q300	J5		



In the above formula, R^a, R^b and R^c are selected from the following Table 23.

Table 23

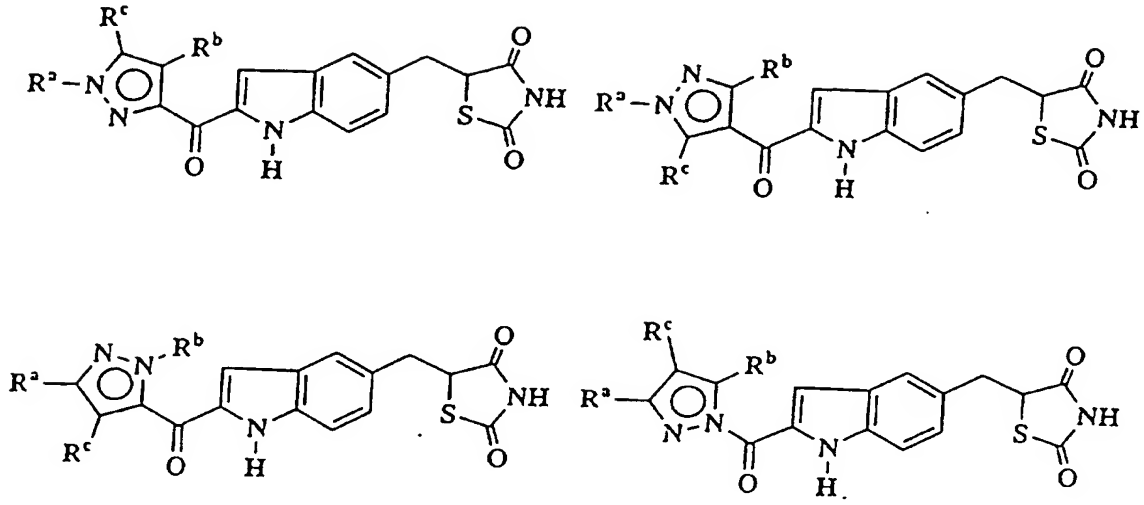
R^a	R^b	R^c	R^a	R^b	R^c
2-Me	H	H	4-Q83	H	H
3-Me	H	H	2-OH	H	H
4-Me	H	H	3-OH	H	H
2-OMe	H	H	4-OH	H	H
3-OMe	H	H	2-F	H	H
4-OMe	H	H	3-F	H	H
2-Ph	H	H	4-F	H	H
3-Ph	H	H	2-Cl	H	H
4-Ph	H	H	3-Cl	H	H
4-Q11	H	H	4-Cl	H	H
4-Q18	H	H	2-Br	H	H
4-Q19	H	H	3-Br	H	H
4-Q49	H	H	4-Br	H	H
4-Q13	H	H	3-CF_3	H	H
4-OPh	H	H			



In the above formula, R^a, R^b and R^c are selected from the following Table 24.

Table 24

R^a	R^b	R^a	R^b	R^a	R^b
H	Me	Q6	Me	Q14	Me
Me	Me	Q85	Me	Q49	Me
Et	Me	Q86	Me	Q76	Me
^{n}Pr	Me	Q87	Me	Q13	Me
^{i}Pr	Me	Q10	Me	OPh	Me
^{t}Bu	Me	Q88	Me	Q83	Me
^{c}Pr	Me	Q89	Me	Ph	H
^{c}Hex	Me	Q8	Me	Ph	Me
Q84	Me	Q90	Me	Ph	Et
Ph	Me	Q91	Me	Ph	^{n}Pr
Q1	Me	4-Ph-Ph	Me	Ph	^{i}Pr
Q2	Me	Q11	Me	Ph	^{t}Bu
Q3	Me	Q12	Me	Ph	^{c}Pr
Q4	Me	Q18	Me	Ph	^{c}Hex
Q5	Me	Q19	Me	Ph	Ph



In the above formula, R^a, R^b and R^c are selected from the following Table 25.

Table 25

R^a	R^b	R^c	R^a	R^b	R^c
H	Me	H	Q90	Me	H
Me	Me	H	Q91	Me	H
Et	Me	H	4-Ph-Ph	Me	H
^{n}Pr	Me	H	Q11	Me	H
^{i}Pr	Me	H	Q12	Me	H
^{t}Bu	Me	H	Q18	Me	H
^{c}Pr	Me	H	Q19	Me	H
^{c}Hex	Me	H	Q14	Me	H
Q84	Me	H	Q49	Me	H
Ph	Me	H	Q76	Me	H
Q1	Me	H	Q13	Me	H
Q2	Me	H	OPh	Me	H
Q3	Me	H	Q83	Me	H
Q4	Me	H	Ph	H	H
Q5	Me	H	Ph	Me	H
Q6	Me	H	Ph	Et	H
Q85	Me	H	Ph	^{n}Pr	H
Q86	Me	H	Ph	^{i}Pr	H
Q87	Me	H	Ph	^{t}Bu	H
Q10	Me	H	Ph	^{c}Pr	H
Q88	Me	H	Ph	^{c}Hex	H
Q89	Me	H	Ph	Ph	H
Q8	Me	H	Ph	Me	Me

As evident from the following test results, the compound (I) or its pharmaceutically acceptable salt of the present invention has a hypoglycemic activity, and can be used alone or in a mixture with a known pharmaceutically acceptable binder, excipient, lubricant or disintegrator, for preventing or treating diabetes mellitus of mammals including humans, mice, rats, rabbits, dogs, monkeys, cows, horses, pigs and the like. The compound (I) or its pharmaceutically acceptable salt of the present invention can also be used for preventing or treating diabetic complications including diabetic eye diseases (such as diabetic cataract and diabetic retinopathy), diabetic neuropathy, diabetic nephropathy, diabetic gangrene, and the like. The compound (I) or its pharmaceutically acceptable salt of the present invention can also be used in combination with various oral hypoglycemic agents such as insulin derivatives, sulfonylurea derivatives and biguanide derivatives, and aldose-reductase inhibitory agents.

The compounds (I) of the present invention may be formulated into various suitable formulations depending upon the manner of administration. The compounds of the present invention may be administered in the form of free thiazolidindione or in the form of physiologically hydrolyzable and acceptable pharmaceutically acceptable salts (such as sodium salts or potassium salts).

The pharmaceutical composition of the present

invention is preferably administered orally in the form of the compound of the present invention by itself or in the form of powders, granules, tablets or capsules formulated by mixing the compound of the present invention with a suitable pharmaceutically acceptable carrier including a binder (such as hydroxypropyl cellulose, syrup, gum arabic, gelatin, sorbitol, tragacanth gum, polyvinyl pyrrolidone or CMC-Ca), an excipient (such as lactose, sugar, corn starch, calcium phosphate, sorbitol, glycine or microcrystal cellulose powder), a lubricant (such as magnesium stearate, talc, polyethylene glycol or silica), and a disintegrator (such as potato starch).

However, the pharmaceutical composition of the present invention is not limited to such oral administration and it is applicable for parenteral administration. For example, it may be administered in the form of e.g. a suppository formulated by using oily base material such as cacao butter, polyethylene glycol, lanolin or fatty acid triglyceride, a transdermal therapeutic base formulated by using liquid paraffin, white vaseline, a higher alcohol, Macrogol ointment, hydrophilic ointment or hydro-gel base material, an injection formulation formulated by using one or more materials selected from the group consisting of polyethylene glycol, hydro-gel base material, distilled water, distilled water for injection and an excipient

such as lactose or corn starch, or a formulation for administration through mucous membranes such as an ocular mucous membrane, a nasal mucous membrane and an oral mucous membrane.

The daily dose of the compound of the present invention is from 0.05 to 50 mg, preferably from 0.1 to 10 mg per kg weight of a patient, and it is administered from once to three times per day. The dose may of course be varied depending upon the age, the weight or the condition of illness of a patient.

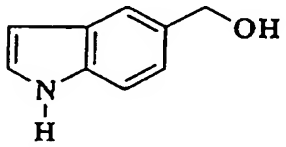
EXAMPLES

Now, the present invention will be described in further detail with reference to Examples for preparation of the compounds of the present invention, Pharmacological Test Examples and Formulation Examples. However, it should be understood that the present invention is by no means restricted by such specific Examples.

Reference 1 Synthesis of hydroxymethylindole (Compound (III))

Synthesis Route 1

Synthesis of 5-hydroxymethylindole (III-1)



(III-1)

10.60 g (65.77 mmol) of 5-indolecarboxylic acid was

dissolved in 120 ml of tetrahydrofuran, and was cooled to 0°C. To the resultant mixture, 9.98 g (263.09 mmol) of lithium aluminum hydride was added little by little. After gradually rising reaction temperature to room temperature, a resultant mixture was heated under reflux for 30 minutes. To the resultant reaction mixture, were added little by little Celite, ethyl acetate, methanol and water in this order, and the mixture was quenched with an excess amount of a reducing agent. A resultant reaction mixture was filtrated by means of a small amount of silica gel. The solvent in the filtrate was removed by distillation under reduced pressure to obtain a 9.50 g (98.1%) of the subject compound (III-1).

Colorless plate-like crystals

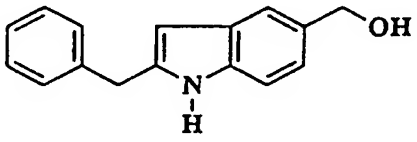
Melting point: 58-58.5°C (solvent for recrystallization: diethylether/hexane)

60MHz ^{1}H-NMR($CDCl_3$), δ :2.10(1H, brs), 4.60(2H, s), 6.35(1H, dd, J=4.0, 3.0Hz), 6.80-7.30(3H, m), 7.41(1H, brs), 8.22(1H, brs).

MS(EI) m/e:147(M^+), 130, 118.

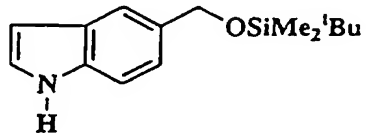
Synthesis route 2

Synthesis of 2-benzyl-5-hydroxymethylindole (III-2)



(III-2)

5-t-butyldimethylsilyloxymethylindole (Compound (VII-1))



(VII-1)

9.50 g (65.55 mmol) of Compound (III-1) was dissolved in 40 ml of dimethylformamide dehydrated with molecular sieves, and 6.96 g (98.325 mmol) of imidazole and 11.85 g (78.66 mmol) of t-butyldimethylsilyl chloride were added thereto and were stirred at room temperature for 10 hours. After finishing the reaction, a saturated sodium chloride aqueous solution was added to the reaction solution, and the mixture was extracted with ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The washed organic phase was then dried with anhydrous sodium sulfate, and the residue obtained after removing a solvent by distillation under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane=1/4). The product thus obtained was further recrystallized to obtain 13.05 g of the subject compound (VII-1).

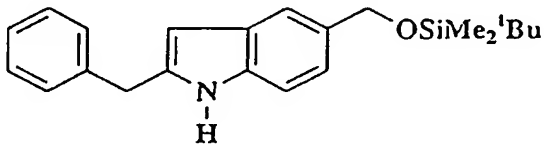
Colorless plate-like crystals

Melting point: 48-49°C (solvent used for recrystallization: diethylether/hexane)

60MHz ^{1}H-NMR($CDCl_3$), δ :0.10(6H, s), 0.92(9H, s), 4.75(2H, s), 6.40(1H, d d, J=4.0, 3.0Hz), 6.92-7.35(3H, m), 7.45(1H, brs), 8.00(1H, brs).

MS(EI) m/e:261(M^+), 246, 204, 130.

2-benzyl-5-t-butyldimethylsilyloxymethylindole (Compound (VII-2))



(VII-2)

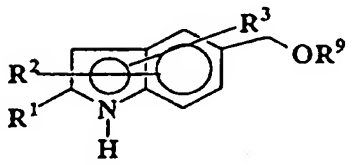
To an anhydrous tetrahydrofuran (5 ml) solution of 555.5 mg (2.1248 mmol) of Compound (VII-1), was dropwise added 1.3 ml (2.1248 mmol) of butyl lithium (1.6 M hexane solution) at -78°C, and the resultant mixture was stirred for 15 minutes. Dry carbon dioxide gas was passed through the reaction solution for 15 minutes. After fully removing carbon dioxide gas at a reaction temperature of 20°C, the reaction temperature was lowered to -78°C. After fully cooling, 2.8 ml (4.2496 mmol) of t-butyl lithium (1.54 M solution in pentane) was dropwise added thereto, and the resultant mixture was stirred for 2 hours. Thereafter, an anhydrous tetrahydrofuran (2 ml) solution of 726.9 mg (4.2496 mmol) of benzylbromide (Compound (VIII-1)) was added thereto at room temperature. After stirring the reaction mixture at -78°C for 30 minutes, the reaction mixture was further stirred at room temperature for 30 minutes and further stirred at a refluxing temperature of a solvent for 15 minutes. After terminating the reaction by adding methylene chloride and 2M hydrochloric acid to the reaction solution, an organic phase obtained was washed

with a saturated ammonium chloride aqueous solution. After drying the organic phase thus obtained with anhydrous sodium sulfate, a residue obtained after removing a solvent by distillation under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/4) and was repeatedly subjected to a silica gel column chromatography (eluent: ethyl acetate/hexane = 1/15) to obtain 111.9 mg (15.0%) of the subject compound (VII-2).

Yellow oily material

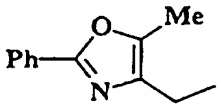
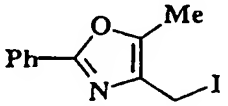
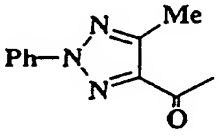
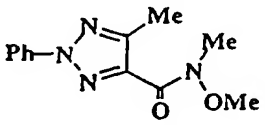
60MHz ^{1}H-NMR($CDCl_3$), δ :0.10(6H, s), 0.92(9H, s), 4.00(2H, s), 4.72(2H, s), 6.18(1H, d, J=2.0Hz), 6.90-7.30(2H, m), 7.38(1H, brs), 7.51(1H, brs).MS (EI) m/e:351(M^+), 294, 235, 220, 149.

In the same manner as above, electrophilic reagents (Compound (VIII)) were used to Compound (VII-1) in place of benzylbromide to synthesize the following compounds (R^1, R^2 and R^3 in the table correspond to the substituents of Compound (VII)).



(VII)

(R^n=H, R^1=W-Z, R^9=$SiMe_2Bu^t$)

Compound No.	R^1	R^2	R^3	Electrophile (VIII)	Properties (mp °C)
VII-3		H	H	 (VIII-2)	Colorless needles (104-105)
VII-4		H	H	 (VIII-3)	Yellow crystals (135-138)

Compound (VII-3)

60MHz ^{1}H-NMR($CDCl_3$), δ :0.90(6H, s), 0.92(9H, s), 2.27(3H, s), 3.96(2H, s), 4.75(2H, s), 6.21(1H, d, J=2.0Hz), 6.90-7.70(6H, m), 7.75-8.15(2H, m), 8.77(1H, brs).

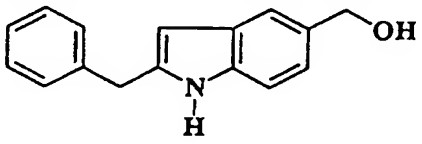
MS(EI) m/e:432(M^+), 417, 375, 301, 156, 105, 75.

Compound (VII-4)

60MHz ^{1}H-NMR($CDCl_3$), δ :1.12(6H, s), 1.95(9H, s), 2.68(3H, s), 4.75(2H, s), 7.00-8.30(9H, m), 9.32(1H, brs).

MS(FD) m/e:446.

2-benzyl-5-hydroxymethylindole (Compound (III-2))



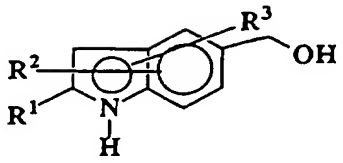
(III-2)

To a tetrahydrofuran (5 ml) solution of 111.9 mg (0.3183 mmol) of Compound (VII-2), was added a tetrahydrofuran (1 ml) solution of 166.4 mg (2.041 mmol) of tetra-n-butylammonium fluoride. After stirring the resultant mixture at room temperature for 3 hours, 166.4 mg (2.041 mmol) of tetra-n-butyl ammonium fluoride was further added thereto and was stirred at room temperature for 2 hours. The resultant reaction solution was extracted by adding 2M-hydrochloric acid, water and chloroform. An organic phase obtained was dried with anhydrous sodium sulfate, and a residue obtained after removing a solvent under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1) to obtain 57.7 mg (76.4%) of the subject compound (III-2).

Yellow crystals

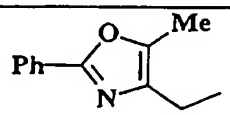
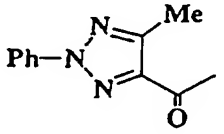
60MHz ^{1}H-NMR($CDCl_3$), δ :1.75(1H, s), 4.00(2H, s), 4.62(1H, s), 6.20(1H, d, J=2.0Hz), 7.00-7.35(2H, m), 7.39(1H, brs), 7.83(1H, brs).

In the same manner as above, Compound (VII-3 and VII-4) were used to synthesize the following compounds (R^1, R^2 and R^3 in the Table correspond to the substituents of Compound (III)).



(III)

(R^n=H, R^1=W-Z)

Compound No.	R^1	R^2	R^3	Properties (mp °C)
III-3		H	H	Pale yellow needles (104-105)
III-4		H	H	Pale yellow needles (225-226)

Compound (III-3)

60MHz ^{1}H-NMR($CDCl_3$), δ : 2.09(1H, brs), 2.22(3H, s), 3.89(2H, s), 4.62(2H, s), 6.18(1H, brs), 6.80-7.60(6H, m), 7.70-8.10(2H, m), 8.92(1H, brs).

MS(EI) m/e:318(M^+), 301, 287, 275, 172, 147, 130, 115, 105, 77.

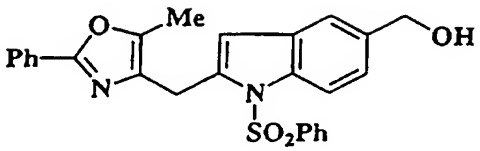
Compound (III-4)

500MHz ^{1}H-NMR(DMSO-d_6), δ : 2.65(3H, s), 4.58(2H, d, J=5.6Hz), 5.15(1H, t, J=5.6Hz), 7.31(1H, dd, J=8.5, 1.0Hz), 7.48(1H, d, J=8.5Hz), 7.53(1H, t, J=7.3Hz), 7.66(2H, t, J=7.3Hz), 7.73(1H, s), 7.96(1H, d, J=1.0Hz), 8.20 (2H, d, J=7.3Hz), 11.92(1H, brs).

MS(EI) m/e:332(M^+), 315, 301, 285, 186, 174, 156, 144, 128, 117, 91, 77.

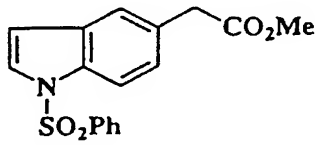
Synthesis Route 3

Synthesis of 1-benzenesulfonyl-5-hydroxymethyl-2-(2-phenyl-5-methyloxazole-4-yl) methylindole (Compound III-5)



(III-5)

Methyl 5-(1-benzenesulfonyl)indolecarboxylate



1.0470 g (6.4966 mmol) of 5-indolecarboxylic acid was dissolved in 10 ml of acetone and was reacted with an excess amount of diazomethane at room temperature. After finishing the reaction, a residue obtained by removing a solvent under reduced pressure was subjected to silica column chromatography (eluent: ethyl acetate/hexane = 1/2) to obtain 1.1123 g (97.7%) of methyl 5-indolecarboxylate.

Colorless crystals

60MHz ^{1}H-NMR($CDCl_3$), δ :3.78(3H, s), 6.52(1H, dd, J=3.0, 3.0Hz), 7.12(1H, d, J=3.0Hz), 7.28(1H, d, J=9.0Hz), 7.82(1H, dd, J=9.0, 2.0Hz), 8.30(1H, d, J=2.0Hz), 8.51(1H, brs).

MS(EI) m/e:175$(M)^+$, 149, 144, 116.

67.8 mg (2.8262 mmol) of sodium hydride was suspended in 2 ml of dimethylformamide dehydrated with molecular sieves. To the suspension thus obtained, was added a molecular sieves-dehydrated dimethylformaldehyde (5 ml) solution of 412.6 mg (2.3552 mmol) of methyl 5-

indolecarboxylate at room temperature. After stirring the resultant mixture for 40 minutes, a molecular sieves-dehydrated dimethylformaldehyde (2 ml) solution of 832.0 mg (4.7104 mmol) of benzenesulfonyl chloride was added thereto at room temperature and was stirred for 2 hours. Water was added to the reaction solution and the reaction solution was extracted with ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The washed organic phase was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was washed with hexane to obtain 729.9 mg (98.3%) of the aimed methyl 5-(1-benzenesulfonyl)indolecarboxylate.

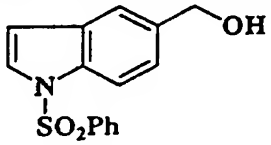
Colorless crystals

Melting point: 149-149.5°C (solvent used for recrystallization: benzene)

60MHz ^{1}H-NMR ($CDCl_3$), δ :3.90(3H, s), 6.67(1H, d, J=5.0Hz), 7.20-8.40(9H, m).

MS(EI) m/e:315(M^+), 284, 174, 159, 143, 115.

1-benzenesulfonyl-5-hydroxymethylindole



508.7 mg (1.6131 mmol) of methyl 5-(1-benzenesulfonyl)indolecarboxylate was dissolved in 5 ml of tetrahydrofuran dehydrated with molecular sieves and

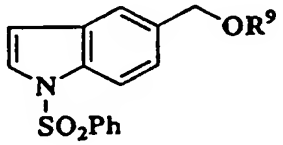
6.32 ml (3.2263 mmol) of diisobutylaluminium hydride (1.02 M toluene solution) was gradually dropwise added thereto at room temperature and the resultant mixture was stirred at room temperature for 30 minutes. To the resultant reaction solution, were added Celite, water and ethylacetate in this order, and the resultant reaction solution was filtrated by a filter paper and the filtrate was washed with a saturated sodium chloride aqueous solution. An organic phase obtained was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was then filtrated by silica gel to obtain 508.8 mg of aimed material. The compound thus obtained was used in the following reaction without further purifying.

Colorless oily material

60MHz ^{1}H-NMR($CDCl_3$), δ :4.65(2H, brs), 6.55(1H, d, J=5.0Hz), 7.00-8.10(9H, m).

MS(EI) m/e:287(M^+), 270, 141, 129, 118, 91, 77.

1-benzenesulfonyl-5-t-butyldimethylsilyloxymethylindole (Compound (VII-5))



(VII-5)

(R^n=SO_2Ph, R^9=$SiMe_2Bu^t$)

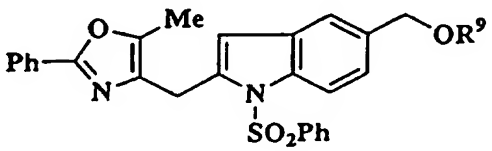
508.8 mg (1.6131 mmol) of 1-benzenesulfonyl-5-hydroxymethylindole was dissolved in 5 ml of dimethylformamide dehydrated with molecular sieves, and

164.7 mg (2.4197 mmol) of imidazole and 486.2 mg (3.2262 mmol) of t-butyldimethysilyl chloride were added thereto and the resultant mixture was stirred at room temperature for 16 hours. After finishing the reaction, the saturated sodium chloride aqueous solution was added to the resultant reaction solution and the resultant reaction solution was extracted with ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The organic phase thus obtained was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was subjected to a silica gel column chromatography (eluent: ethyl acetate/hexane = 1/4) to obtain 611.9 mg (94.5%) of the subject compound (VII-5)

Colorless oily material

60MHz ^{1}H-NMR($CDCl_3$), δ :0.07(6H, s), 0.90(9H, s), 4.70(2H, s), 7.00-8.00 (9H, m).

1-benzenesulfonyl-2-(2-phenyl-5-methyloxazole-4-yl)methyl-5-t-butyldimethylsilyloxymethylindole (Compound (VII-6))



(VII-6)
(R^n=SO_2Ph, R^9=$SiMe_2Bu^t$)

To an anhydrous tetrahydrofuran (2 ml) solution of 167.1 mg (0.4161 mmol) of Compound (VII-5), was dropwise

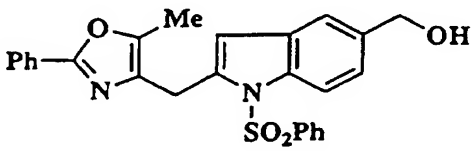
added 0.35 ml (0.5409 mmol) of t-butyllithium (1.54 M solution in pentane) at -12°C. After rising the reaction temperature to room temperature, the reaction mixture was stirred for 30 minutes, and 248.9 mg (0.8322 mmol) of 2-phenyl-5-methyloxazole-4-ylmethyl iodide (Compound (VIII-2)) and anhydrous tetrahydrofuran (2 ml) solution were added thereto at room temperature. After stirring the mixture for 1 hour, water was added to the reaction solution and the reaction solution was extracted with ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The organic phase thus obtained was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was subjected to a silica gel column chromatography (eluent: ethyl acetate/hexane = 1/7) repeatedly to obtain 160.9 mg (67.5%) of the subject compound (VII-6).

Light-yellow oily material

60MHz ^{1}H-NMR($CDCl_3$), δ :0.12(6H, s), 0.90(9H, s), 2.22(3H, s), 4.22(2H, s), 4.72(2H, s), 6.27(1H, s), 6.80-8.20(13H, m).

MS(EI) m/e:572(M^+), 515, 441, 374, 299, 105.

1-benzenesulfonyl-2-(2-phenyl-5-methyloxazole-4-yl)methyl-5-hydroxymethylindole (Compound (III-5))



(III-5)
(R^n=SO_2Ph)

To a tetrahydrofuran (1 ml) solution of 46.9 mg (0.0819 mmol) of Compound (VII-6), was added 0.5 ml of tetran-butylammonium fluoride (1M THF solution). After stirring the resultant mixture for 1 hour at room temperature, the water was added to the resultant reaction solution and the reaction solution was extracted with chloroform. An organic phase obtained was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/2) to obtain quantitatively 39.5 mg of the subject compound (III-5).

Light-yellow oily material

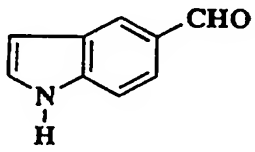
60MHz ^{1}H-NMR($CDCl_3$), δ :3.22(3H, s), 4.22(2H, s), 4.66(2H, s), 6.28(1H, s), 6.80-8.30(13H, m).

MS(EI) m/e:458(M^+), 317, 300, 287, 245, 217, 195, 154, 105, 77.

Reference Example 2 Synthesis of formylindole (Compound II)

Synthesis Route 1

Synthesis of 5-formylindole (II-a-1)



(II-a-1)

750.2 mg (5.0971 mmol) of 5-hydroxymethylindole (Compound (III-1)) was dissolved in 14 ml of

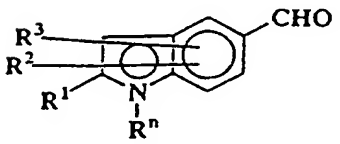
tetrahydrofuran, and 4.4314 g (50.971 mmol) of activated manganese dioxide was added thereto and the resultant mixture was heat-refluxed for 17 hours. After the reaction mixture was filtrated to remove an oxidizing agent residue, yellow brown crystals (657.0 mg) obtained were subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1) to obtain 602.6 mg (81.4%) of the subject compound (II-a-1)

Light yellow crystals Melting point: 95-96°C

60MHz ^{1}H-NMR($CDCl_3$), δ :6.50(1H, dd, J=3.0, 2.0Hz), 7.18(1H, d, J=3.0Hz), 7.36(1H, d, J=9.0Hz), 7.68(1H, dd, J=9.0, 1.0Hz), 8.05(1H, brs), 8.75(1H, brs), 9.90(1H s).

MS(EI) m/e:145$(M)^+$, 116, 89.

In the same manner as above, the following compounds were synthesized (R^1, R^2, R^3 and R^n in the table correspond to the substituents of Compound (II)).



(II-a)

Compound No.	R^1	R^2	R^3	R^n	Starting material (III)	Properties (mp °C)
II-a-2	2-(Ph-ethyl)	H	H	H	III-2	Yellow crystals (108-109)
II-a-3	2-(Ph-oxazole-Me-ethyl)	H	H	H	III-3	Pale yellow crystals (127-128)
II-a-4	2-(Ph-triazole-Me-acetyl)	H	H	H	III-4	Pale yellow powder (258.5-259.5)
II-a-5	2-(Ph-oxazole-Me-ethyl)	H	H	SO_2Ph	III-5	Yellow amorphous

Compound (II-a-2)

60MHz ^{1}H-NMR($CDCl_3$), δ :4.08(2H, s), 6.36(1H, brs), 6.88-7.50(6H, m), 7.58(1H, dd, J=9.0, 2.0Hz), 7.97(1H, brs), 8.30(1H, brs), 9.85(1H, s).

MS(EI) m/e:235(M^+), 206, 158, 129, 115, 102, 91, 77.

Compound (II-a-3)

60MHz ^{1}H-NMR($CDCl_3$), δ :2.27(3H, s), 3.92(2H, s), 6.35(1H, brs), 7.10-8.05(8H, m), 9.55(1H, brs), 9.81(1H, s).

MS(EI) m/e: 316(M^+), 287, 273, 170, 115, 105, 77.

Compound (II-a-4)

500MHz ^{1}H-NMR(DMSO-d_6), δ : 2.67(3H, s), 7.54(1H, t, J=7.3Hz), 7.66(1H, d, J=9.8Hz), 7.70(2H, t, J=7.8Hz), 7.84(1H, dd, J=9.8, 1.0Hz), 8.21(2H, d, J=7.8Hz), 8.24(1H, s), 8.49(1H, d, J=1.0Hz), 10.02(1H, s, -CHO), 12.47 (1h, brs).

MS(EI) m/e:330(M^+), 301, 172, 117, 91, 77.

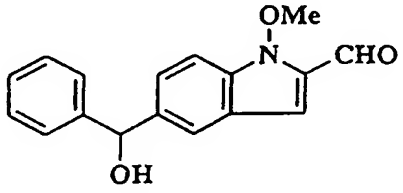
Compound (II-a-5)

60MHz ^{1}H-NMR($CDCl_3$), δ :2.27(3H, s), 4.26(2H, s), 6.42(1H, s), 7.10-8.40 (13H, m), 9.92(1H, s).

MS(EI) m/e:456(M^+), 315, 105, 77.

Synthesis Route 2

Synthesis of 2-formyl-5-(1-hydroxybenzyl)-1-methoxyindole (Compound (II-a-6))



(II-b-6)

2-formylindole (Compound (II-b)) can be obtained by conducting formylation at the 2-position of 5-bromo-1-methoxyindole synthesized through 5-boromoindoline using 5-bromoindole as a starting material.

1.09 g (5.5598 mmol) of 5-bromoindole was dissolved in 20 ml of acetic acid, and 2.1 g (33.3 mmol) of sodium cyanoborohydride was added little by little thereto at room temperature. After stirring the resultant mixture at room temperature for 20 minutes, acetic acid was

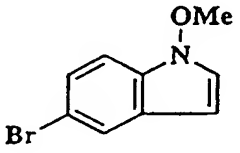
removed by distillation. 40% sodium hydroxide was then added thereto, and the resultant reaction solution was completely neutralized with acetic acid and was extracted with ethyl acetate. After an organic phase obtained was dried with anhydrous sodium sulfate, a residue obtained by removing a solvent by distillation under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 2/1) to obtain 904.2 mg (82.1%) of 5-boromoindoline.

Colorless oily material

60MHz ^{1}H-NMR($CDCl_3$), δ :2.90(2H, brt, J=8.0Hz), 3.42(2H, brt, J=8.0Hz) 3.42(1H, brs), 6.30(1H, d, J=9.0Hz), 6.95(1H, dd, J=9.0, 2.0Hz), 7.01(1H, d, J=2.0Hz).

MS(EI) m/e:199(M^+), 197(M^+), 117, 89.

5-bromo-1-methoxyindole (Compound (IX-1))



(IX-1)

904 2 mg (4.565 mmol) of 5-bromoindoline was converted by the method disclosed in "Heterocycles" by M. Somei and T. Kawasaki, 1989, 29, 1251 to 739.3 mg (3.2701 mmol, 71.6%) of the subject compound (IX)-1).

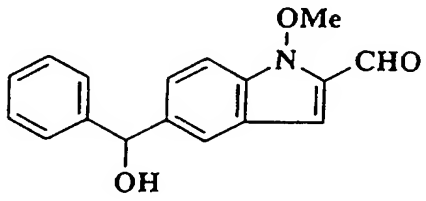
Colorless column-like crystals

Melting point: 44-45°C

500MHz ^{1}H-NMR($CDCl_3$), δ :4.08(3H, s), 6.29(1H, d, J=3.4Hz), 7.25(1H, d, J=3.4Hz), 7.31(1H, brs), 7.71(1H, brs).

MS(EI) m/e:227(M^+), 225(M^+) 212, 210, 196, 194, 115, 88.

2-formyl-5-(1-hydroxybenzyl)-1-methoxyindole (Compound (II-b-6))



(II-b-6)

To an anhydrous tetrahydrofuran (5 ml) solution of 492.9 mg (2.1802 mmol) of Compound (IX-1), was dropwise added 2.35 ml of phenyl lithium (1.02 M solution in ether-cyclohexane, 2.3982 mmol) at -16°C under argon atmosphere. After 15 minutes, 159.4 mg (2.1802 mmol) of anhydrous dimethylformamide was added thereto. After the resultant mixture was stirred at -16°C for 15 minutes as it was, the reaction temperature was lowered to -78°C. After fully lowering the reaction temperature, 2.02 ml of t-butyl lithium (1.61 M solution in pentane, 3.2703mmol) was dropwise added thereto. After 10 minutes, 0.66 ml (6.5406 mmol) of benzaldehyde (Compound (VIII-4)) was added thereto, and the resultant mixture was stirred for 10 minutes. 20 ml of water was added to the resultant reaction mixture, and the reaction mixture was extracted with ethyl acetate to obtain an organic phase. The organic phase thus obtained was washed with a saturated sodium chloride aqueous solution, and the washed organic phase was dried with anhydrous sodium sulfate. Thereafter, the residue obtained by removing a solvent by

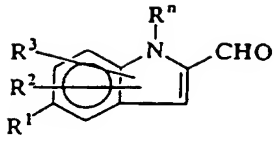
distillation under reduced pressure was subjected to a silica gel column chromatography (eluent: ethyl acetate/hexane = 1/3) to obtain 494.7 mg (80.7%) of the subject compound (II-b-6).

Light-yellow oily material

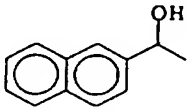
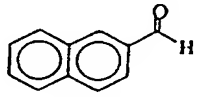
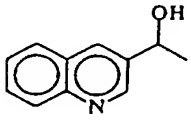
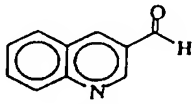
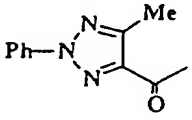
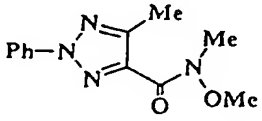
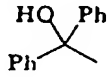
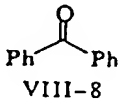
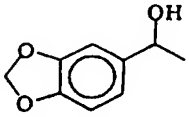
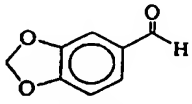
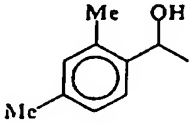
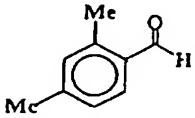
500MHz ^{1}H-NMR($CDCl_3$), δ :2.32(1H, brs), 4.15(3H, s), 5.95(1H, s), 7.09(1H, d, J=0.7Hz), 7.28(1H, brt, J=8.0Hz), 7.35(2H, brt, J=8.0Hz), 7.41(2H, brd, J=8.0Hz), 7.43(1H, dd, J=9.0, 1.5Hz), 7.46(1H, ddd, J=9.0, 1.5, 0.7Hz), 7.73(1H, dd, J=1.5, 0.7Hz), 9.90(1H, s).

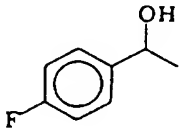
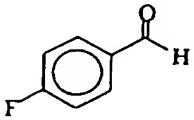
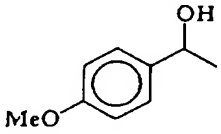
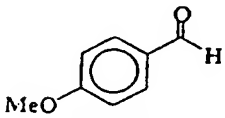
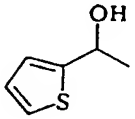
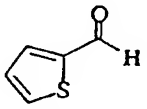
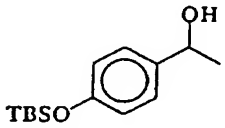
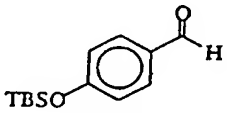
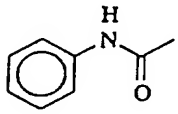
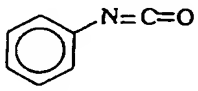
MS(EI) m/e: 281(M^+), 264, 176, 148, 117, 105, 77.

In the same manner as above, electrophilic reagents (Compound (VIII)) were used in place of benzaldehyde to synthesize the following compounds (R^1, R^2, R^3 and Z in the table correspond to the substituent of Compound (II-b)).



(II-b)

Compound No.	R^1	R^2	R^3	R^n	Electrophile (VIII)	Properties (mp °C)
II-b-7		H	H	MeO	 VIII-5	Yellow oil
II-b-8		H	H	MeO	 VIII-6	Pale yellow plates (168-168.5)
II-b-9		H	H	MeO	 VIII-3	Colorless needles (176.5-177.5, decomp.)
II-b-10		H	H	MeO	 VIII-8	Pale yellow plates (147-148)
II-b-11		H	H	MeO	 VIII-9	Yellow oil
II-b-12		H	H	MeO	 VIII-10	Yellow oil

Compound No.	R^1	R^2	R^3	R^n	Electrophile (VIII)	Properties (mp °C)
II-b-13		H	H	MeO	 VIII-11	Yellow oil
II-b-14		H	H	MeO	 VIII-12	Yellow oil
II-b-15		H	H	MeO	 VIII-13	Yellow oil
II-b-16		H	H	MeO	 VIII-14	Yellow oil
II-b-17		H	H	MeO	 VIII-15	Pale yellow needles (162.5-163.5)

Compound (II-b-7)

500MHz ^{1}H-NMR($CDCl_3$), δ :2.39(1H, brs), 4.15(3H, s), 6.12(1H, brs), 7.09 (1H, s), 7.40-7.52(4H, m), 7.72-7.80(3H, m), 7.94(1H, brs), 9.91(1H, s).

MS(EI) m/e: 331(M^+), 314, 299, 283, 270, 254, 241, 226, 215, 202, 172, 155, 127, 116, 101, 89.

Compound (II-b-8)

500MHz ^{1}H-NMR(DMSO-d_6), δ :4.09(3H, s), 6.10(1H, d, J=3.9Hz), 6.29(1H, d, J=3.9Hz), 7.35(1H, s), 7.51(1H, d, J=8.0Hz), 7.55(1H, d, J=8.0Hz), 7.59 (1H, dd, J=8.0, 8.0Hz), 7.71(1H, dd, J=8.0, 8.0Hz), 7.89(1H, s), 7.98(1H, d, J=9.0Hz), 7.99(1H, d, J=9.0Hz), 8.33(1H, brs), 8.90(1H, d, J=1.0Hz), 9.91(1H, s).

MS(EI) m/e: 332(M^+), 315, 255, 245, 202, 156, 128, 117.

Compound (II-b-9)

500MHz ^{1}H-NMR($CDCl_3$), δ :2.72(3H, s), 4.24(3H, s), 7.32(1H, s), 7.41(1H, brt, J=7.6Hz), 7.52(2H, brt, J=7.6Hz), 7.63(1H, dd, J=8.8, 0.7Hz), 8.12 (2H, brd, J=7.6Hz), 8.39(1H, dd, J=8.8, 1.5Hz), 8.86(1H, dd, J=1.5, 0.7Hz), 9.98(1H, s).

MS(EI) m/e: 360(M^+), 329, 310, 202, 186, 172, 143, 115, 91, 77.

Compound (II-b-10)

500MHz ^{1}H-NMR($CDCl_3$), δ :2.86(1H, brs), 4.17(3H, s), 7.04(1H, s), 7.26-7.37(10H, m), 7.45-7.48(2H, m), 7.50-7.52(1H, m), 9.89(1H, s).

MS(EI) m/e: 357(M^+), 280, 249, 220, 202, 183, 165, 143, 116, 105, 89, 77.

Compound (II-b-11)

500MHz ^{1}H-NMR($CDCl_3$), δ :2.25(1H, brs), 4.16(3H, s), 5.87(1H, brs), 5.93 (1H, d, J=1.0Hz), 5.94(1H, d, J=1.0Hz), 6.78(1H, d, J=7.8Hz), 6.88(1H, dd, J=7.8, 1.0Hz), 7.10(1H, s), 7.42 (1H, dd, J=8.6, 1.0Hz), 7.47 (1H, d, J=8.6Hz), 7.73 (1H, d, J=1.0Hz), 9.91 (1H, s).

MS(EI) m/e: 325(M^+), 308, 277, 202, 172, 149, 122, 93.

Compound (II-b-12)

500MHz ^{1}H-NMR($CDCl_3$), δ :2.15 (1H, brs), 2.24 (3H, s), 2.32 (3H, s,), 4.16 (3H, s,), 6.08 (1H, brs), 6.99 (1H, brs), 7.07 (1H, brs), 7.08 (1H, brd, J=8.3Hz), 7.42 (1H, brd, J=8.3Hz), 7.42 (1H, brd, J=8.3Hz), 7.46 (1H, brd, J=8.3Hz), 7.64 (1H, brs), 9.90(1H, s).

MS(EI) m/e: 309(M^+), 293, 231, 219, 181, 169, 133, 131, 119, 104, 69.

Compound (II-b-13)

500MHz ^{1}H-NMR($CDCl_3$), δ :2.30 (1H, brd, J=3.4Hz), 4.16(3H, s), 5.94 (1H, brd, J=3.4Hz), 7.03 (2H, dd, J=8.6, 8.6Hz), 7.10 (1H, d, J=0.5Hz), 7.37 (2H, dd, J=10.5, 8.6Hz), 7.40 (1H, dd, J=8.5, 1.5Hz), 7.48 (1H, ddd, J=8.5, 0.7, 0.5Hz), 7.71 (1H, dd, J=1.5, 0.7Hz), 9.91(1H, s).

MS(EI) m/e: 299(M^+), 123.

Compound (II-b-14)

500MHz ^{1}H-NMR($CDCl_3$), δ :2.24 (1H, brs), 3.80 (3H, s), 4.16 (3H, s), 5.92 (1H, s), 6.88 (2H, brd, J=8.8Hz), 7.10 (1H, d, J=0.9Hz), 7.31 (2H, brd, J=8.8Hz), 7.42 (1H, dd, J=8.8, 1.5Hz), 7.46 (1H, ddd, J=8.8, 0.9, 0.9Hz), 7.74 (1H, dd, J=1.5, 0.9Hz), 9.91 (1H, s).

MS(EI) m/e: 311(M^+), 294, 263, 202, 135.

Compound (II-b-15)

400MHz ^{1}H-NMRR($CDCl_3$), δ :2.53 (1H, brs), 4.18 (3H, s), 6.95-7.00 (2H, m), 7.12 (1H, brs), 7.26-7.32 (1H, m), 7.52 (2H, brs), 7.81 (1H, brs), 9.92 (1H, s).

MS(EI) m/e: 287(M^+), 270, 239, 223, 202, 171, 143, 111.

Compound (II-b-16)

500MHz ^{1}H-NMR($CDCl_3$), δ :0.18 (6H, s), 0.97 (9H, s), 2.27 (1H, brs), 4.16 (3H, s), 5.90 (1H, brs), 6.81 (2H, brd, J=8.5Hz), 7.09 (1H, d, J=0.5Hz), 7.23 (2H, brd, J=8.5Hz), 7.42 (1H, dd, J=8.9, 1.0Hz), 7.46 (1H, ddd, J=8.9, 0.5, 0.5Hz), 7.72 (1H, dd, J=1.0, 0.5Hz), 9.90 (1H, s).

MS(EI) m/e: 411(M^+), 354, 323, 305, 294, 266, 235, 201, 150, 135.

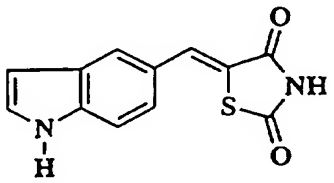
Compound (II-b-17)

400MHz ^{1}H-NMR(DMSO-d_6), δ :4.17 (3H, s), 7.10 (1H, brt, J=7.5Hz), 7.36 (2H, brt, J=7.5Hz), 7.54 (1H, d, J=0.9Hz), 7.73 (1H, dddd, J=8.8, 1.6, 0.9, 0.7Hz), 7.80 (2H, brd, J=7.5Hz), 8.07 (1H, dd, J=8.8, 1.6Hz), 8.49 (1H, dd, J=1.6, 0.7Hz), 9.99 (1H, s), 10.32 (1H, brs).

MS(EI) m/e: 294(M^+), 202, 171, 143, 115, 92, 65.

EXAMPLE 1

Synthesis of 5-(5-indolylmethylidene)thiazolidine-2,4-dione (Compound (I-1a-1)) (Step A)



(I-1a-1)

To a toluene (10 ml) solution of 548.7 mg (3.7800 mmol) of Compound (II-1), were added a toluene (0.5 ml) solution of 96.6 mg (1.134 mmol) of piperidine and 885.5 mg (7.56 mmol) of thiazolidine-2,4-dione and a toluene (0.5 ml) solution of 45.4 mg (0.756 mmol) of acetic acid, and the resultant mixture was heat-refluxed for 1 hour. Orange color crystals were precipitated from the reaction

solution, and the crystals were filtrated and were dissolved in acetone. The solution thus obtained was heated with activated carbon, and methanol was added thereto and a solvent was then removed by distillation under reduced pressure. Crystals precipitated were filtrated and dried to obtain 400.8 mg (43.4%) of the aimed material (compound (I-1a-1)).

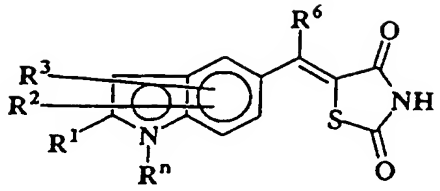
Yellow crystals

Melting point: 320-325°C (dec.) (solvent used for recrystallization: methanol/acetone)

60MHz ^{1}H-NMR(DMSO-d_6), δ :6.50(1H, m), 7.21(1H, dd, J=9.0, 2.0Hz), 7.38(1H, d, J=5.0Hz), 7.45(1H, d, J=9.0Hz), 7.75(1H, d, J=2.0Hz), 7.79(1H, s), 11.40(2H, brs).

MS(EI) m/e:244(M^+), 173, 145, 128.

In the same manner as above, the following compounds were synthesized (R^1, R^2, R^3 and R^n and the table correspond to the substituents of Compound (I-1a)).



(I-1a)

(R^4,R^7=bond , R^6=H)

Compound No.	R^1	R^2	R^3	R^n	Starting material (II)	Properties (mp °C)
I-1a-2	2-(Ph-)	H	H	H	II-a-2	Yellow powder (269-270, decomp.)
I-1a-3	2-(Ph-oxazole-Me)	H	H	H	II-a-3	Orange powder (265)
I-1a-4	2-(Ph-triazole-Me-O)	H	H	H	II-a-4	Yellow powder (315-318, decomp.)
I-1a-5	2-(Ph-oxazole-Me)	H	H	SO_2Ph	II-a-5	Pale yellow powder (260, decomp.)

Compound (I-1a-2)

500MHz ^{1}H-NMR(DMSO-d_6), δ :4.09(2H, s), 6.28(1H, s), 7.20-7.35(6H, m), 7.41(1H, d, J=8.5Hz), 7.70(1H, d, J=1.0Hz), 7.85(1H, s), 11.38(1H, brs), 12.38(1H, brs).

MS(FAB$^+$) m/e:335(M$^+$), 263, 218.

Compound (I-1a-3)

500MHz ^{1}H-NMR(DMSO-d_6), δ :2.73(3H, s), 4.02(2H, s), 6.34(1H, s), 7.27(1H, dd, J=8.5, 1.0Hz), 7.45(1H, d, J=8.5Hz), 7.43-7.55(3H, m), 7.73(1H, d, J=1.0Hz), 7.86(1H, s), 7.92(2H, dd, J=5.8, 1.0Hz), 11.36(1H, brs), 12.43(1H, brs).

MS(EI) m/e:416(M$^+$), 344, 172.

Compound (I-1a-4)

500MHz ^{1}H-NMR(DMSO-d_6), δ :2.66(3H, s), 7.54(1H, brt, J=8.0Hz), 7.57(1H, d, J=8.8Hz), 7.64(1H, brd, J=8.8Hz), 7.67(2H, brt, J=8.0Hz), 7.87(1H, s), 8.12(1H, s), 8.14(1H, s), 8.21(2H, brd, J=8.0Hz), 12.31(1H, brs), 12.50 (1H, brs).

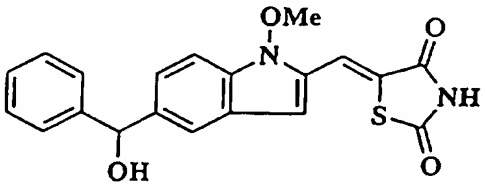
MS(FD) m/e:429(M^+).

Compound (I-1a-5)

500MHz ^{1}H-NMR(DMSO-d_6), δ :2.32(3H, s), 4.29(2H, s), 6.58(1H, s), 7.45-7.65(5H, m), 7.68(1H, t, J=7.0Hz), 7.74(1H, d, J=1.0Hz), 7.82(1H, s), 7.87 -8.00(4H, m), 8.18(1H, d, J=8.8Hz), 12.56(1H, brs).

MS(EI) m/e:555(M^+), 414, 353, 141, 105.

To an ethanol (8 ml) solution of 494.7 mg (1.7586 mmol) of compound (II-b-6), were added 412.0 mg (3.5171 mmol) of thiazolidine-2,4-dione and 29.9 mg (0.3517 mmol) of piperidine. A resultant mixture was heat-refluxed for 3 hours, and the reaction solution was cooled. Crystals precipitated were filtrated and dried to obtain 465.9 mg (69.6%) of the aimed compound (I-1b-6).



(I-1b-6)

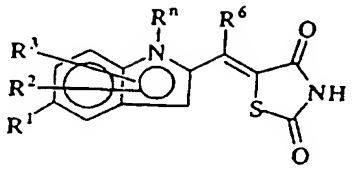
Yellow needle-like crystals

Melting point: 222-223°C (dec.) (solvent used for recrystallization: chloroform/ethanol)

500MHz ^{1}H-NMR(DMSO-d_6), δ :4.07(3H, s), 5.79(1H, d, J=3.9Hz), 5.89(1H, d, J=3.9Hz), 6.75(1H, s), 7.20(1H, brt, J=7.5Hz), 7.30(2H, brt, J=7.5Hz), 7.33(1H, dd, J=8.5, 1.0Hz), 7.40(2H, brd, J=7.5Hz), 7.48(1H, d, J=8.5Hz), 7.69(1H, s), 7.71(1H, d).

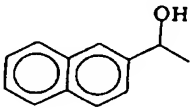
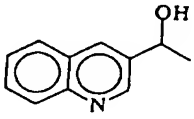
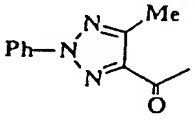
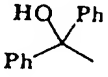
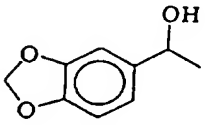
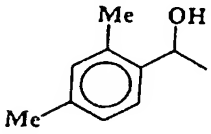
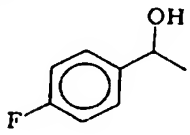
MS(EI) m/e:380(M^+), 349, 306, 205, 105.

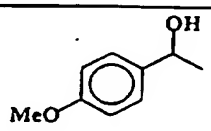
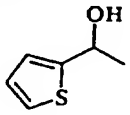
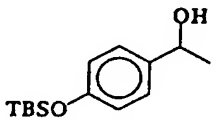
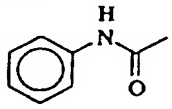
In the same manner as above, the following compounds were synthesized (R^1, R^2, R^6 and R^n correspond to the substituents of Compound (I-1b)).



(I-1b)

(R^4,R^7=bond , R^6=H)

Compound No.	R^1	R^2	R^3	R^n	Starting material (II)	Properties (mp °C)
I-1b-7		H	H	MeO	II-b-7	Orange powder (226-227)
I-1b-8		H	H	MeO	II-b-8	Yellow crystals (260-265, decomp.)
I-1b-9		H	H	MeO	II-b-9	Orange powder (260-261, decomp.)
I-1b-10		H	H	MeO	II-b-10	Orange amorphous
I-1b-11		H	H	MeO	II-b-11	Orange powder (300-350, decomp.)
I-1b-12		H	H	MeO	II-b-12	Yellow powder (178-179, decomp.)
I-1b-13		H	H	MeO	II-b-13	Yellow needles (224-225, decomp.)

Compound No.	R^1	R^2	R^3	R^n	Starting material (II)	Properties (mp °C)
I-1b-14		H	H	MeO	II-b-14	Orange needles (219-220, decomp.)
I-1b-15		H	H	MeO	II-b-15	Orange powder (>224, decomp.)
I-1b-16		H	H	MeO	II-b-16	Yellow needles (111-113)
I-1b-17		H	H	MeO	II-b-17	Yellow powder (200-207, decomp.)

Compound (I-1b-7)

500MHz ^{1}H-NMR(DMSO-d_6), δ :4.06(3H, s), 5.97(1H, d, J=3.0Hz), 6.05(1H, d, J=3.0Hz), 6.76(1H, s), 7.30-8.00(11H, m), 12.65(1H, brs).

MS(EI) m/e:430(M^+), 301, 254, 220, 205, 155, 127, 91.

Compound (I-1b-8)

500MHz ^{1}H-NMR(DMSO-d_6), δ :4.07(3H, s), 6.08(1H, d, J=3.4Hz), 6.25(1H, d, J=3.4Hz), 7.41(1H, s), 7.38-8.90(10H, m), 12.66(1H, brs).

MS(EI) m/e:431(M^+), 400, 357, 330, 301, 255, 216, 200, 172, 156, 128.

Compound (I-1b-9)

500MHz ^{1}H-NMR(DMSO-d_6), δ :2.62(3H, s), 4.18(3H, s), 7.07(1H, s), 7.50(1H, brt, J=7.6Hz), 7.63(2H, brt, J=7.6Hz), 7.71(1H, s), 7.74(1H, d, J=8.8Hz), 8.10(2H, brd, J=7.6Hz), 8.18(1H, dd, J=8.8, 1.0Hz), 8.78(1H, d, J=1.0Hz), 12.83(1H, brs).

MS(EI) m/e:459(M^+), 385, 357, 225, 199, 171, 143, 127, 91.

Compound (I-1b-10)

500MHz ^{1}H-NMR($CDCl_3$), δ :3.05 (1H, brs), 4.09 (3H, s), 6.58 (1H, s), 7.20 -7.50 (13H, m), 7.91 (1H, s), 8.90 (1H, brs).

MS(EI) m/e:456(M^+), 379, 177, 149, 105, 77.

Compound (I-1b-11)

500MHz ^{1}H-NMR(DMSO-d_6), δ :4.07(3H, s), 5.71 (1H, d, J=4.0Hz), 5.84 (1H, d, J=4.0Hz), 5.94 (1H, d, J=0.5Hz), 5.95 (1H, d, J=0.5Hz), 6.75 (1H, s), 6.82 (1H, d, J=8.9Hz), 6.87 (1H, dd, J=8.9, 1.0Hz), 6.90 (1H, d, J=1.0Hz), 7.32 (1H, dd, J=8.5, 1.0Hz), 7.47 (1H, d, J=8.5Hz), 7.69 (2H, s), 12.65 (1H, brs).

MS(EI) m/e:424(M^+), 228, 213, 102.

Compound (I-1b-12)

500MHz ^{1}H-NMR(DMSO-d_6), δ :2.16 (3H, s), 2.24 (3H, s), 4.07 (3H, s), 5.69 (1H, d, J=3.8Hz), 5.87 (1H, d, J=3.8Hz), 6.75 (1H, s), 6.91 (1H, brs), 7.01 (1H, brd, J=7.6Hz), 7.26 (1H, dd, J=8.5, 1.0Hz), 7.39 (1H, d, J=7.6Hz), 7.47 (1H, d, J=8.5Hz), 7.58 (1H, brs), 7.69 (1H, s), 12.65 (1H, brs).

MS(EI) m/e:408(M^+), 379, 358, 275, 205, 172, 133, 105.

Compound (I-1b-13)

500MHz ^{1}H-NMR(DMSO-d_6), δ :4.07(3H, s), 5.80 (1H, d, J=3.8Hz), 5.96 (1H, d, J=3.8Hz), 6.75 (1H, s), 7.12 (2H, t, J=8.3Hz), 7.32 (1H, dd, J=8.6, 1.2Hz), 7.42 (2H, dd, J=8.3, 5.7Hz), 7.48 (1H, d, J=8.6, 0.5Hz), 7.70 (1H, dd, J=1.2, 0.5Hz), 12.65 (1H, brs).

MS(FAB$^+$) m/e:398(M^+).

Compound (I-1b-14)

500MHz ^{1}H-NMR(DMSO-d_6), δ :3.38 (3H, s), 4.07 (3H, s), 5.74 (1H, d, J=3.8Hz), 5.80 (1H, d, J=3.8Hz), 6.74 (1H, brs), 6.85 (2H, d, J=8.8Hz), 7.28 (2H, d, J=8.8Hz), 7.31 (1H, dd, J=8.6, 1.0Hz), 7.47 (1H, dd, J=8.6, 0.5Hz), 7.68 (1H, dd, J=1.0, 0.5Hz), 7.69 (1H, s), 12.65 (1H, brs).

MS(EI) m/e:410(M^+), 220, 205, 172, 135, 108, 77.

Compound (I-1b-15)

500MHz ^{1}H-NMR(DMSO-d_6), δ :4.09 (3H, s), 6.02 (1H, d, J=4.5Hz), 6.23 (1H, d, J=4.5Hz), 6.78 (1H, s), 6.88 (1H, dd, J=4.0, 0.4Hz), 6.92 (1H, dd, J=5.0, 4.0Hz), 7.38 (1H, dd, J=5.0, 0.4Hz), 7.40 (1H, dd, J=8.6, 0.3Hz), 7.51 (1H, d, J=8.6Hz), 7.70 (1H, s), 7.75 (1H, d, J=0.3Hz), 12.65 (1H, brs).

MS(EI) m/e:386(M^+), 301, 256, 205, 171, 145, 111, 85.

Compound (I-1b-16)

400MHz ^{1}H-NMR(DMSO-d_6), δ :0.15 (6H, s), 0.93 (9H, s), 4.07 (3H, s), 5.72 (1H, d, J=3.7Hz), 5.82 (1H, d, J=3.7Hz), 6.75 (1H, s), 6.77 (2H, d, J=8.4Hz), 7.25 (2H, d, J=8.4Hz), 7.32 (1H, brd, J=8.3Hz), 7.47 (1H, brd, J=8.3Hz), 7.68 (1H, s), 7.69 (1H, brs), 12.09 (1H, brs).

MS(EI) m/e:510(M^+), 422, 378, 205.

Compound (I-1b-17)

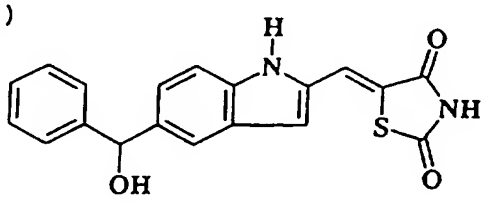
400MHz ^{1}H-NMR(DMSO-d_6), δ :4.17(3H, s), 6.93 (1H, s), 7.11 (1H, brt, J=7.3Hz), 7.35 (2H, brt, J=7.3Hz), 7.69 (1H, d, J=8.8Hz), 7.72 (1H, s), 7.80 (2H, brd, J=7.3Hz), 7.96 (1H, d, J=8.8Hz), 8.40 (1H, brs), 10.28 (1H, brs), 12.70 (1H, brs).

MS(EI) m/e:393(M^+), 301, 270, 230, 199, 171, 127, 92, 65.

EXAMPLE 2

Removal of substituent R^n (Step C)

Synthesis of 5-((5-(1-hydroxybenzyl)indole-2-yl)methylidene)thiazolidine-2,4-dione (Compound (I-1b-101))



(I-1b-101)

To a tetrahydrofuran-water (12 ml-4 ml) solution of 455.9 mg (1.1984 mmol) of compound (I-1b-6), were added 489.1 mg of magnesium oxide and 476.8 mg of 10% Pd-C, and the resultant mixture was stirred for 20 hours at room temperature under hydrogen atmosphere of 1 atmospheric pressure. After terminating the reaction, the reducing agent was removed by filtration. The solvent in the filtrate was removed by distillation under reduced pressure, and a residue obtained was recrystallized to obtain 409.4 mg (97.5%) of the subject compound (I-1b-101).

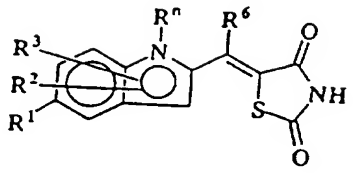
Yellow powder

Melting point: 450°C< (solvent used for recrystallization: THF/benzene)

500MHz ^{1}H-NMR(DMSO-d_6), δ : 5.77(1H, d, J=3.9Hz), 5.82(1H, d, J=3.9Hz), 6.77(1H, s,), 7.18 (1H, brt, J=9.0Hz), 7.21(1H, d, J=9.0Hz), 7.28(2H, brt, J=9.0Hz), 7.36(1H, d, J=9.0Hz), 7.39(2H, brd, J=9.0Hz), 7.65(1H, s), 7.72(1H, s), 11.59(1H, brs), 12.52(1H, brs).

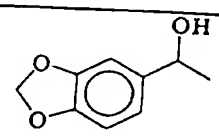
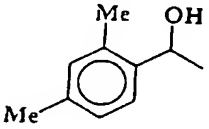
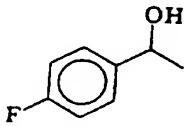
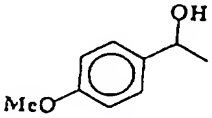
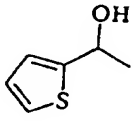
MS(EI) m/e:350(M^+), 279, 220, 205, 145, 105, 91, 77.

In the same manner as above, the following compounds were synthesized (R^1, R^2, R^3 and R^n in the table correspond to the substituents of Compound (I-1b)).



(I-1b)

(R^4,R^7=bond , R^6=H)

Compound No.	R^1	R^2	R^3	R^n	Starting material (I-1b)	Properties (mp °C)
I-1b-102		H	H	H	I-1b-11	Yellow powder (330-400, decomp.)
I-1b-103		H	H	H	I-1b-12	Yellow powder (125-160, decomp.)
I-1b-104		H	H	H	I-1b-13	Yellow powder (246-250, decomp.)
I-1b-105		H	H	H	I-1b-14	Yellowish orange powder (280-300, decomp.)
I-1b-106		H	H	H	I-1b-15	Yellow powder (280-290, decomp.)

Compound (I-1b-102)

500MHz ^{1}H-NMR(DMSO-d_6), δ :5.68 (1H, d, J=3.9Hz), 5.77 (1H, d, J=3.9Hz), 5.93 (1H, d, J=0.5Hz), 5.95 (1H, d, J=0.5Hz), 6.78 (1H, d, J=1.0Hz), 6.81 (1H, d, J=8.0Hz), 6.86 (1H, dd, J=8.0, 1.0Hz), 6.89 (1H, d, J=1.0Hz), 7.20 (1H, dd, J=8.6, 1.0Hz), 7.36 (1H, d, J=8.6Hz)7.63 (1H, d, J=1.0Hz), 7.74 (1H, s), 11.59 (1H, s), 12.50 (1H, brs).

MS(FD$^+$) m/e:394(M^+).

Compound (I-1b-103)

500MHz ^{1}H-NMR(DMSO-d_6), δ :2.14 (3H, s), 2.24 (3H, s), 5.62 (1H, d, J=5.0 Hz), 5.86 (1H, d, J=5.0Hz), 6.77 (1H, s), 6.90 (1H, s), 7.01 (1H, brd, J=6.9Hz), 7.14 (1H, brd, J=8.1Hz), 7.36 (1H, d, J=8.1Hz), 7.39 (1H, d, J=6.9Hz), 7.52 (1H, s), 7.73 (1H, s), 11.59 (1H, brs), 12.50 (1H, brs).

MS(FAB$^+$) m/e:379(M^++1), 362.

Compound (I-1b-104)

500MHz ^{1}H-NMR(DMSO-d_6), δ :5.78 (1H, d, J=3.8Hz), 5.89 (1H, d, J=3.8Hz), 6.78 (1H, dd, J=1.0, 0.3Hz), 7.11 (2H, t, J=9.0Hz), 7.20 (1H, dd, J=5.1, 1.0Hz), 7.37 (1H, dd, J=5.1, 0.5, 0.3Hz), 7.40 (2H, dd, J=9.0, 6.1Hz), 7.65 (1H, dd, J=1.0, 0.5Hz), 7.74 (1H,s), 11.61 (1H, brs), 12.52 (1H,brs).

MS(FAB$^+$) m/e:368(M^++1).

Compound (I-1b-105)

500MHz ^{1}H-NMR(DMSO-d_6), δ :3.71 (3H, s), 5.71 (1H, d, J=3.8Hz), 5.73 (1H, d, J=3.8Hz), 6.78 (1H, dd, J=1.0, 0.5Hz), 6.85 (2H, d, J=8.5Hz), 7.19 (1H, dd, J=8.5, 1.0Hz), 7.27 (2H, d, J=8.5Hz), 7.35 (1H, ddd, J=8.5, 0.5, 0.5Hz), 7.63 (1H, dd, J=1.0, 0.5Hz), 7.74 (1H,s), 11.59 (1H,brs), 12.50 (1H, brs).

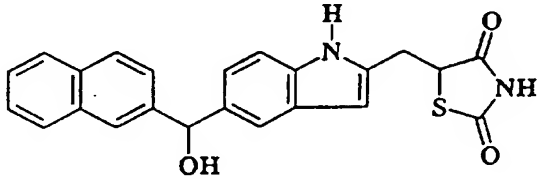
MS(FAB$^+$) m/e:381(M^++1), 380, 363.

Compound (I-1b-106)

500MHz ^{1}H-NMR(DMSO-d_6), δ :5.99 (1H, d, J=4.2Hz), 6.16 (1H, d, J=4.2Hz), 6.81 (1H, dd, J=1.0, 0.5Hz), 6.85 (1H, dd, J=4.0, 1.0Hz), 6.92 (1H, dd, J=5.1, 4.0Hz), 7.28 (1H, dd, J=8.8, 1.0Hz), 7.37 (1H, dd, J=5.1, 1.0Hz), 7.40 (1H, ddd, J=8.8, 0.7, 0.5Hz), 7.69 (1H, dd, J=1.0, 0.5Hz), 7.75 (1H, s), 11.64 (1H,brs), 12.52 (1H, brs).

MS(EI) m/e:356(M^+), 340, 286, 269, 245, 174, 143, 116, 99, 44.

Compound (I-1b-7) was reduced in the same manner as above, and compound (I-2b-5) wherein the substituent R^n was removed and the connecting part between an indole ring and a thiazole ring was reduced, was formed.



(I-2b-5)

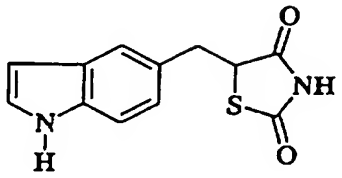
Light-yellow powder

Melting point: 100-108°C (solvent used for recrystallization: chloroform/hexane)

500MHz ^{1}H-NMR(DMSO-d_6), δ : 3.26(1H, dd, J=15.4, 9.8Hz), 3.50(1H, dd, J=15.4, 3.9Hz), 4.94(1H, dd, J=9.8, 3.9Hz), 5.82(1H, d, J=3.9Hz), 5.90(1H, d, J=3.9Hz), 6.18(1H, s), 7.00-8.00(10H, m), 10.97(1H, s), 12.07(1H, brs).

EXAMPLE 3

Synthesis of 5-(indole-ylmethyl)thiazolidine-2,4-dione (Compound (I-2a-1)) (Step B)



(I-2a-1)

EXAMPLE 3-1 Reduction by hydrogenation

To a tetrahydrofuran (10 ml) solution of 104.7 mg (0.4286 mmol) of compound (I-1a-1), was added 109.7 mg of 10% Pd-C, and the resultant mixture was stirred at room temperature for 20 hours under hydrogen atmosphere of 1 atmospheric pressure. After finishing the reaction, the reducing agent was removed by filtration. The solvent in the filtrate was removed by distillation under reduced pressure, and a residue obtained was dissolved in a solvent of ethyl acetate/hexane (1/1). This solution was filtrated by silica gel, and was subjected to recrystallization to obtain 80.8 mg of the aimed compound (I-2a-1).

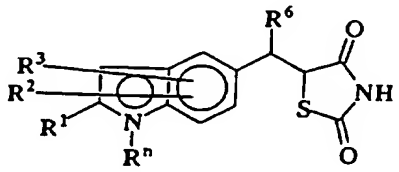
Yellow column-like crystals

Melting point: 159.5-160.5°C (solvent used for recrystallization: ethylacetate/hexane)

60MHz ^{1}H-NMR(CD_3COCD_3), δ :3.15(1H, dd, J=12.0, 9.0Hz), 3.60(1H, dd, J=12.0, 5.0Hz), 4.70(1H, dd, J=9.0, 5.0Hz), 6.31(1H, m), 6.90-7.60(4H, m), 10.00(1H, brs).

MS(EI) m/e:246(M^+), 130, 115.

In the same manner as above, the following compounds were synthesized (R^1, R^2, R^3 and R^n in the table correspond to the substituents of Compound (I-2a)).



(I-2a)

(R^4,R^7=H , R^6=H)

Compound No.	R^1	R^2	R^3	R^n	Starting material (I-1a)	Properties (mp °C)
I-2a-2	2-(Ph-ethyl)	H	H	H	I-1a-2	Yellow prisms (132-133)
I-2a-3	2-(Ph-oxazole-Me-ethyl)	H	H	H	I-1a-3	Pale yellow powder (111-112)
I-2a-4	2-(Ph-oxazole-Me-ethyl)	H	H	SO_2Ph	I-1a-5	Pale yellow prisms (104-105)
I-2a-7	2-(Ph-triazole-Me-acetyl)	H	H	H	I-1a-4	Pale yellow crystals (115-116)

Compound (I-2a-2)

500MHz ^{1}H-NMR($CDCl_3$), δ :3.19(1H, dd, J=14.1, 10.1Hz), 3.63(1H, dd, J=14.1, 3.9Hz), 4.13(2H, s), 4.57(1H, dd, J=10.1, 3.9Hz), 6.30(1H, dd, J=1.0, 0.5Hz), 6.97(1H, dd, J=8.3, 1.7Hz), 7.20(1H, ddd, J=8.3, 0.5, 0.5Hz), 7.21-7.27(5H, m), 7.39(1H, dd, J=0.5, 0.5Hz), 7.77 (1H, brs), 7.79 (1H, brs).

MS(FAB$^+$) m/e:337(M^+), 220.

Compound (I-2a-3)

500MHz ^{1}H-NMR(DMSO-d_6), δ :2.35(3H, s), 3.10(1H, dd, J=7.5, 5.0Hz), 3.42 (1H, dd, J=7.5, 2.5Hz), 3.97(2H, s), 4.88(1H, dd, J=5.0, 2.5Hz), 6.14(1H, s), 6.89(1H, dd, J=8.0, 1.0Hz), 7.23(1H, d, J=8.0Hz), 7.27(1H, d, J=1.0 Hz), 7.45-7.55(3H, m), 7.91(2H, dd, J=8.0, 2.0Hz), 10.90(1H, brs), 11.96 (1H, brs).

MS(FAB$^+$) m/e:418(M$^+$), 301, 172.

Compound (I-2a-4)

500MHz ^{1}H-NMR($CDCl_3$), δ :2.30(3H, s), 3.18(1H, dd, J=15.0, 10.0Hz), 3.56 (1H, dd, J=15.0, 5.0Hz), 4.25(2H, s), 4.52(1H, dd, J=10.0, 5.0Hz), 6.31 (1H, s), 7.12(1H, dd, J=8.0, 2.0Hz), 7.30-7.50(6H, m), 7.52(1H, dd, J=8. 0, 8.0Hz), 7.78(2H, dd, J=7.0, 1.0Hz), 7.82(1H, brs), 7.97-8.02(2H, m), 8.11(1H, d, J=8.0Hz).

MS(EI) m/e:557(M$^+$), 416, 386, 299.

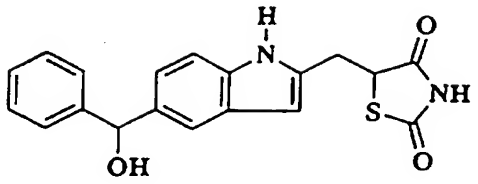
Compound (I-2a-7)

500MHz ^{1}H-NMR($CDCl_3$), δ :2.65 (3H, s), 3.21 (1H, dd, J=14.2, 8.8Hz), 3.48 (1H, dd, J=14.2, 4.4Hz), 4.95 (1H, dd, J=8.8, 4.4Hz), 7.23 (1H, brd, J= 8.5), 7.46 (1H, brd, J=8.5Hz), 7.52 (1H, brt, J=7.6Hz), 7.66 (1H, brs), 7.97 (1H, brs), 8.20 (1H, brt, J=7.6Hz), 11.96 (1H, brs), 12.01 (1H, brs).

MS(EI) m/e:431(M$^+$), 415, 205, 183, 156, 129, 91.

EXAMPLE 3-2 Reduction by amalgam

Synthesis of 5-((5-(1-hydroxybenzyl)indole-2-yl)methyl)thiazolidine-2,4-dione (Compound (I-2a-6))



(I-2b-6)

To a MeOH (3 ml) solution of 119.0 mg (0.3396 mmol) of compound (I-1b-6), was added 3% sodium-amalgam, and the resultant mixture was stirred at room temperature for 18 hours. After finishing the reaction, the reaction mixture was filtrated to remove the reducing agent. The solvent in the filtrate was removed by distillation under reduced pressure, and a residue obtained was subjected to silica gel column chromatography (eluent: tetrahydrofuran/benzene=1/3) to obtain 86.0 mg (61.1%) of the subject compound (I-2b-6).

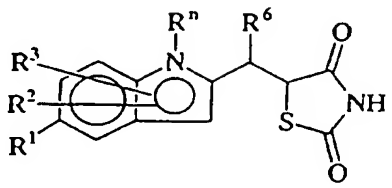
Colorless powder

Melting point: 84-87°C (solvent used for recrystallization: chloroform/hexane)

500MHz ^{1}H-NMR($CDCl_3$), δ :3.42(1H, dd, J=15.4, 7.3Hz), 3.53(1H, dd, J=15.4, 4.9Hz), 4.60(1H, dd, J=7.3, 4.9Hz), 5.95(1H, d, J=2.0Hz), 6.35(1H, d, J=7.8Hz), 7.25(1H, brt, J=7.6Hz), 7.28(1H, d, J=7.6Hz), 7.33(2H, brt, J=7.6Hz), 7.42(2H, brd, J=7.6Hz), 7.56(1H, s), 7.95(1H, brs), 8.26(1H, brs).

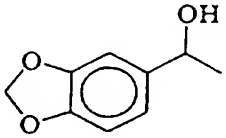
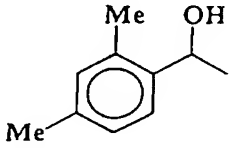
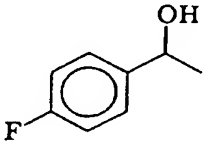
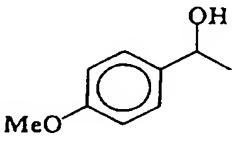
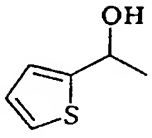
MS(EI) m/e:352(M^+), 236, 205, 105, 78.

In the same manner as above, the following compounds were synthesized (R^1, R^2, R^3 and R^n in the table correspond to the substituents of Compound (I-2b)).



(I-2b)

(R^4,R^7=bond , R^6=H)

Compound No.	R^1	R^2	R^3	R^n	Starting material (I-1b)	Properties (mp °C)
I-2b-8		H	H	H	I-1b-102	Pale yellow amorphous
I-2b-9		H	H	H	I-1b-103	Yellow powder (102-104)
I-2b-10		H	H	H	I-1b-104	Pale yellow powder (77-81)
I-2b-11		H	H	H	I-1b-105	Pale yellow powder (75-77, decomp.)
I-2b-12		H	H	H	I-1b-106	Pale yellow powder (68-69, decomp.)

Compound (I-2b-8)

500MHz ^{1}H-NMR(DMSO-d_6), δ :3.25 (1H, dd, J=15.2, 10.0Hz), 3.51 (1H, dd, J=15.2, 3.6Hz), 4.94 (1H, dd, J=10.0, 3.6Hz), 5.63 (1H, d, J=4.5Hz), 5.64 (1H, d, J=4.5Hz), 5.92 (1H, brs), 5.93 (1H, brs), 6.18 (1H, brs), 6.79 (1H, d, J=8.0Hz), 6.83 (1H, dd, J=8.0, 1.0Hz), 6.88 (1H, d, J=1.0Hz), 7.01 (1H, brd, J=8.5Hz), 7.20 (1H, brd, J=8.5Hz), 7.41 (1H, brs), 10.96 (1H, brs), 12.07 (1H, brs).

MS(EI) m/e:396(M^++1), 280, 149.

Compound (I-2b-9)

500MHz ^{1}H-NMR(DMSO-d_6), δ :2.12 (3H, s), 2.23 (3H, s), 3.24 (1H, dd, J=17.5, 9.5Hz), 3.51 (1H, dd, J=17.5, 5.0Hz), 4.95 (1H, dd, J=9.5, 5.0Hz), 5.46 (1H, d, J=4.5Hz), 5.81 (1H, d, J=4.5Hz), 6.16 (1H, brs), 6.88 (1H, brs), 6.95 (1H, brd, J=8.0Hz), 6.99 (1H, brd, J=8.0Hz), 7.20 (1H, brd, J=8.0Hz), 7.31 (1H, brs), 7.41 (1H, brd, J=8.0Hz), 10.97 (1H, brs), 12.09 (brs).

MS(FAB$^+$) m/e:381(M^++1), 364.

Compound (I-2b-10)

500MHz ^{1}H-NMR(DMSO-d_6), δ :3.27 (1H, dd, J=15.4, 9.8Hz), 3.51 (1H, dd, J=15.4, 4.2Hz), 4.95 (1H, dd, J=9.8, 4.2Hz), 5.73 (1H, d, J=3.9Hz), 5.75 (1H, d, J=3.9Hz), 6.18 (1H, brs), 7.00 (1H, brd, J=8.3Hz), 7.08 (2H, J=8.8Hz), 7.21 (1H, brd, J=8.3Hz), 7.39 (2H, dd, J=8.8, 5.8Hz), 7.42 (1H, brs), 10.89 (1H, brs), 12.09 (1H, brs).

MS(FAB$^+$) m/e:371(M^++1), 370, 353, 307, 254.

Compound (I-2b-11)

500MHz ^{1}H-NMR(DMSO-d_6), δ :3.70 (3H, s), 5.58 (1H, d, J=3.9Hz), 5.67 (1H, d, J=3.9Hz), 6.17 (1H, brs), 6.83 (2H, d, J=9.5Hz), 7.00 (1H, brd, J=4.3Hz), 7.20 (1H, brd, J=4.3Hz), 7.26 (2H, d, J=9.5Hz), 7.40 (1H, brs), 10.96 (1H, brs), 12.07 (1H, brs).

MS(FAB$^+$) m/e:382(M$^+$), 365, 266, 249, 135, 119.

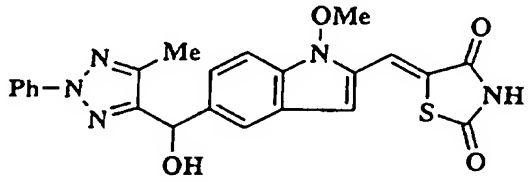
Compound (I-2b-12)

500MHz ^{1}H-NMR(DMSO-d_6), δ :3.27 (1H, dd, J=15.0, 10.0Hz), 3.52 (1H, dd, J=15.0, 3.9Hz), 4.96 (1H, dd, J=10.0, 3.9Hz), 5.94 (1H, d, J=4.2Hz), 6.02 (1H, d, J=4.2Hz), 6.20 (1H, brs), 6.82 (1H, dd, J=3.4, 1.2Hz), 6.90 (1H, dd, J=5.3, 3.4Hz), 7.09 (1H, brd, J=8.3Hz), 7.25 (1H, brd, J=8.3Hz), 7.33 (1H, dd, J=5.3, 1.2Hz), 7.48 (1H, brs), 11.03 (1H, brs), 12.10 (1H, brs).

MS(FAB$^+$) m/e:358(M$^+$), 341, 242.

EXAMPLE 4

Synthesis of 5-((1-methoxy-5-hydroxy(2-phenyl-5-methyl-1,2,3-triazol-4-yl)methylindol-2-yl)methylidenethiazolidine-2,4-dione (Compound (I-1b-18))



(I-1b-18)

To a tetrahydrofuran (5 ml) solution of 129.8 mg (0.2825 mmol) of compound (I-1b-9), was added 21.4 mg (0.5650 mmol) of sodium borohydride at room temperature, and the resultant mixture was stirred for 1 hour. After finishing the reaction, water and 2M hydrochloric acid

were added to the reaction solution and the reaction solution was extracted with a mixed solvent of chloroform: MeOH=9:1. An organic phase obtained was washed with a saturated sodium chloride aqueous solution, and a solvent was removed by distillation under reduced pressure. A residue obtained was recrystallized from chloroform/hexane to obtain 127.9 mg (98.1%) of Compound (I-1b-18).

Orange crystals

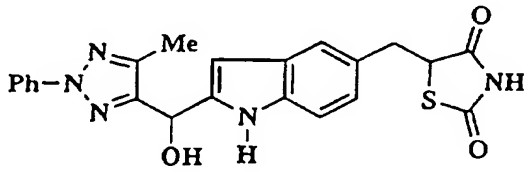
Melting point: 170-176°C (decomposition) (solvent used for recrystallization: chloroform/hexane)

500MHz ^{1}H-NMR(DMSO-d_6), δ :2.21 (3H, s), 4.07 (3H, s), 6.08 (1H, d, J=4.3 Hz), 6.19 (1H, d, J=4.3Hz), 6.79 (1H, s), 7.35 (1H, brt, J=7.5Hz), 7.40 (1H, d, J=8.0Hz), 7.53 (2H, brt, J=7.5Hz), 7.45 (1H, d, J=8.0Hz), 7.68 (1H, s), 7.27 (1H, brs), 7.93 (2H, brt, J=7.5Hz), 12.63 (1H, brs).

MS(EI) m/e:461(M^+), 431, 387, 362, 331, 301, 186, 172, 117.

EXAMPLE 5

Synthesis of 5-((2-hydroxy(2-phenyl-5-methyl-1,2,3-tiazol-4-yl)methylindol-5-yl)methyl)thiazolidine-2,4-dione (Compound (I-2a-19))



(I-2a-19)

To a tetrahydrofuran (3 ml) solution of 100.5 mg (0.2329 mmol) of Compound (I-2a-7), was added 26.4 mg

(0.6988 mmol) of sodium borohydride at room temperature, and the resultant mixture was stirred for 3 hours. After finishing the reaction, water and 2M hydrochloric acid were added to the reaction solution and the reaction solution was extracted with a mixed solvent of chloroform: MeOH=9:1. An organic layer obtained was washed with a saturated sodium chloride aqueous solution, and a solvent was removed by filtration under reduced pressure. A residue obtained was recrystallized with chloroform-hexane, and the recrystallized material was subjected to silica gel column chromatography (eluent: tetrahydrofuran/hexane = 1/2) and was further recrystallized from chloroform-hexane to obtain 14.8 mg (14.7%) of Compound (I-2a-19).

Colorless crystals

Melting point: 103-108°C(decomposition) (solvent used for recrystallization: chloroform/hexane)

500MHz ^{1}H-NMR(DMSO-d_6), δ :3.10 (1H, dd, J=14.0, 9.8Hz), 3.44 (1H, dd, J=14.1, 4.2Hz), 4.89 (1H, dd, J=9.8, 4.2Hz), 6.13 (1H, d, J=4.6Hz), 6.22 (1H, brs), 6.28 (1H, d, J=4.6Hz), 6.93 (1H, brd, J=8.3Hz), 7.28 (1H, brd, J=8.3Hz), 7.32 (1H, brs), 7.73 (1H, brt, J=7.8Hz), 7.53 (2H, brt, J=7.8Hz), 7.95 (2H, brd, J=7.8Hz), 11.05 (1H, brs), 11.97 (1H, brs).

MS(EI) m/e:433(M^+), 315, 299, 187, 158, 130.

20 mg (0.0479 mmol) of Compound (I-2a-3) was dissolved in 2 ml of a methanol/tetrahydrofuran mixture solution (1/1 v/v). 2.57 ml of sodium hydroxide aqueous solution (74.7 mg%) was added to the above prepared

solution of Compound (I-2a-3), and the resultant mixture was stirred at room temperature for 1 hour and 20 minutes. Thereafter, a solvent was removed by distillation under reduced pressure and an aqueous solution of a residue obtained was freeze-dried to obtain 16.4 mg (77.9%) of Compound (I-4a-1).

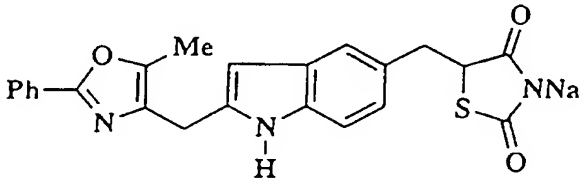
Colorless crystals

Melting point: 260-265°C (decomposition)

MS(FAB$^+$) m/e: 439(M^+)

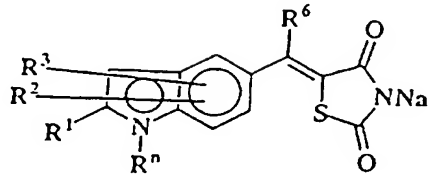
EXAMPLE 6

Preparation of sodium salt of 5-(((2-phenyl-5-methyl-1,2,3-triazol-4-yl)methylindol-5-yl)methyl)thiazolidine-2,4-dione (Compound (I-4a-1))



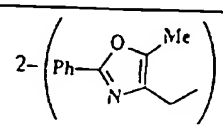
(I-4a-1)

In the same manner as above, the following compounds were synthesized (R^1, R^2, R^3 and R^n in the table correspond to the substituents of Compounds (I-3a, I-4a, I-3b and I-4b)).



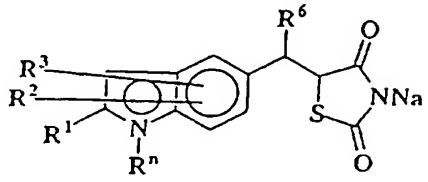
(I-3a)

(R^4,R^7=H , R^6=H)

Compound No.	R^1	R^2	R^3	R^n	Starting materials (I-1a)	Properties (mp °C)
I-3a-1		H	H	SO_2Ph	I-1a-5	Colorless amorphous (160-180, decomp.)

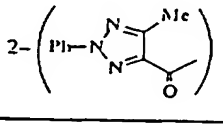
Compound (I-3a-1)

MS(FAB$^+$) m/e:578(M^++1).



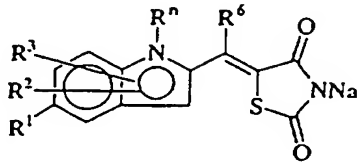
(I-4a)

(R^4,R^7=H , R^6=H)

Compound No.	R^1	R^2	R^3	R^n	Starting materials (I-2a)	Properties (mp °C)
I-4a-2		H	H	H	I-2a-7	Yellow powder (180-250, decomp.)

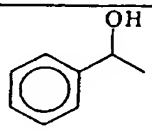
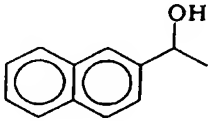
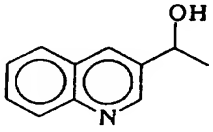
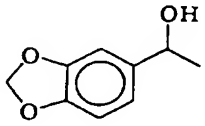
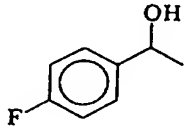
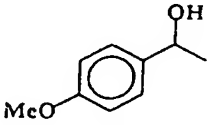
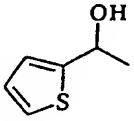
Compound (I-4a-2)

MS(FD) m/e:476(M^++Na), 454(M^++1), 431(M^+-Na+1).



(I-3b)

(R^4,R^7=bond , R^6=H)

Compound No.	R^1	R^2	R^3	R^n	Starting materials (I-1b)	Properties (mp °C)
I-3b-2		H	H	MeO	I-1b-6	Yellow amorphous (220-230, decomp.)
I-3b-3		H	H	MeO	I-1b-7	Yellow amorphous (260-280, decomp.)
I-3b-4		H	H	MeO	I-1b-8	Yellow amorphous (195-230, decomp.)
I-3b-5		H	H	MeO	I-1b-11	Yellow amorphous (180-230, decomp.)
I-3b-6		H	H	MeO	I-1b-13	Yellow amorphous (172-176, decomp.)
I-3b-7		H	H	MeO	I-1b-14	Yellow amorphous (164-170, decomp.)
I-3b-8		H	H	MeO	I-1b-15	Yellow amorphous (240-260, decomp.)

Compound (I-3a-2)

MS(FAB$^+$) m/e:403(M^++1).

Compound (I-3a-3)

MS(FAB$^+$) m/e:403(M^++1).

Compound (I-3a-5)

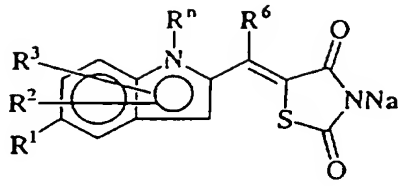
MS(FD) m/e:424(M^+-Na+1).

Compound (I-3a-7)

MS(FD) m/e:410(M^+-Na+1).

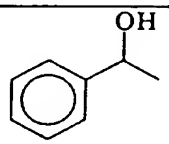
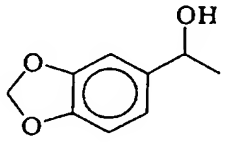
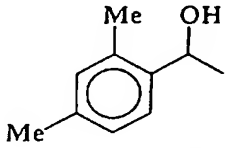
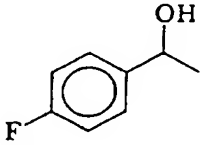
Compound (I-3a-8)

MS(FAB$^+$) m/e:387(M^+-Na+1), 386.



(I-3b)

(R^4,R^7=bond , R^6=H)

Compound No.	R^1	R^2	R^3	R^n	Starting materials (I-1b)	Properties (mp °C)
I-3b-9		H	H	H	I-1b-101	Yellow crystals (220-400, decomp.)
I-3b-10		H	H	H	I-1b-102	Yellow crystals (200-400, decomp.)
I-3b-11		H	H	H	I-1b-103	Yellow amorphous (190-210, decomp.)
I-3b-12		H	H	H	I-1b-104	Colorless amorphous (190-220, decomp.)

Compound (I-3b-9)

MS(FAB$^+$) m/e:395(M^++Na), 373.

Compound (I-3b-10)

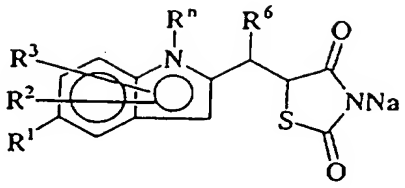
MS(FAB$^+$) m/e:439(M^++Na), 417, 416.

Compound (I-3b-11)

MS(FAB$^+$) m/e:423(M^++Na), 401(M^++1), 400(M^+).

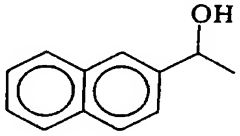
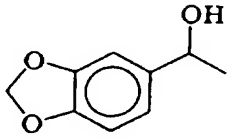
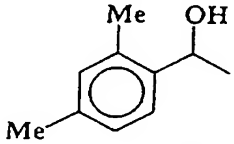
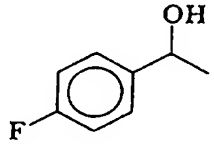
Compound (I-3b-12)

MS(FAB$^+$) m/e:412(M^++Na-1), 390(M^+).



(I-4b)

(R^4,R^7=bond , R^6=H)

Compound No.	R^1	R^2	R^3	R^n	Starting materials (I-2b)	Properties (mp °C)
I-4b-3		H	H	H	I-2b-5	Pale brown crystals (180-300, decomp.)
I-4b-4		H	H	H	I-2b-8	Pale red amorphous (200-300, decomp.)
I-4b-5		H	H	H	I-2b-9	Yellow amorphous (210-290, decomp.)
I-4b-6		H	H	H	I-2b-10	Colorless amorphous

Compound (I-4b-3)

MS(FD) m/e:447(M^++Na), 425(M^++1).

Compound (I-4b-4)

MS(FD) m/e:441(M^++Na), 419(M^++1).

Compound (I-4b-5)

MS(FD) m/e:425(M^++Na), 403(M^++1).

Compound (I-4b-6)

MS(FAB^+) m/e:414(M^++Na).

TEST EXAMPLE 1: Measurement of hypoglycemic effect

KK mouse and KKA^y mouse, NIDDM models (male, 6-7 weeks old) (Nakamura, Proc. Jpn. Acad., vol. 38, 348-352, 1962; Iwatsuka et al. Endocrinol. Jpn., vol. 17, 23-35, 1970) were purchased from Nihon Clea. They were allowed free access to high-calories' chow (CMF, Oriental Yeast) and water. Around 40 g-weighted mice were examined.

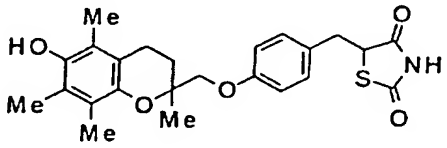
Blood (20 $\mu\ell$) collected from the retro-orbital sinus was diluted in 60 units heparin sodium-solution and was centrifuged in a microfuge. The supernatant was assayed. The glucose concentration was determined by glucose oxidase method (Glucose Analyzer II, Beckman). A group of 3 to 4 mice having a blood glucose value of higher than 200 mg/dℓ, the blood glucose value of which did not reduce by more than 10% for 24 hours after once oral administration of 0.5% carboxymethyl cellulose (CMC)-saline, were tested.

All test-compounds suspended in 0.5% carboxy-methyl cellulose (CMC)-saline were orally administered in mice.

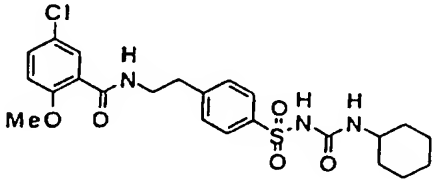
Before and 24 hours after the administration, blood was collected from the retro-orbital sinus, and a blood glucose value was measured in the above-mentioned manner. The hypoglycemic activity was expressed by the percentage of reducing blood glucose calculated before and 24 hours after the administration.

KKA^{y} mouse

Compound No.	Dose (mg/kg)	% decrease
I-1a-1	30	17.6
I-1a-3	30	23.4
I-1a-4	30	26.5
I-1b-7	30	14.2
I-1b-13	30	12.7
I-1b-14	30	23.8
I-1b-17	30	17.5
I-1b-18	30	22.6
I-1b-103	30	14.1
I-1b-105	30	19.6
I-2a-1	30	16.0
I-2a-2	30	27.9
I-2a-4	30	15.1
I-2b-6	30	38.0
I-2b-8	30	10.8
I-2b-10	30	20.9
I-2a-19	30	32.2
I-3b-5	30	25.0
I-3b-8	30	18.8
I-3b-9	30	17.5
I-3b-12	30	17.0
I-4a-1	30	28.0
I-4b-5	30	28.4
CS-045	30	-3.0
Glibenclamide	30	-2.5



CS-045



Glibenclamide

The compounds of the present invention exhibited hypoglycemic activities at substantially higher degree as compared with CS-045 used as controls. Glibenclamide (insulin-releasing agent) did not exhibit hypoglycemic activity in this test.

TEXT EXAMPLE 2: Measurement of hypoglycemic and hypolipidemic effect

db/db mice, NIDDM model (male 6 weeks old), were purchased from Nihon Charles River. They were allowed free access to chow (MF, Oriental Yeast) and water. Around 50 g-weighed mice were examined.

Blood (20 μl) collected from the retro-orbital sinus was diluted in 60 units heparin sodium-solution and was centrifuged in a microfuge. The supernatant was assayed. The glucose concentration was determined by glucose oxidase method (Glucose Analyzer II, Beckman). A group of 6 mice were tested.

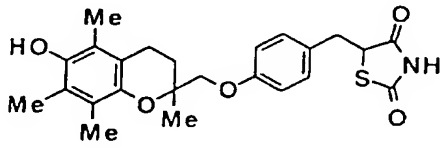
All test-compounds suspended in 0.5% carboxy-methyl cellulose (CMC)-saline were orally administered in mice once a day for 4 days. Before, 1 day, 2 days, 3 days and 4 days after the administration, blood was collected from the retro-orbital sinus, and a blood glucose value was measured in the above-mentioned manner. The hypoglycemic activity was expressed by the percentage of reducing blood glucose calculated before and 1 day, 2 days, 3 days or 4 days after the administration.

The total cholesterol (TC) amounts in bloods

collected before drug-administration and 4 days after the drug-administration were measured in accordance with the cholesterol oxidase method and the triglyceride (TG) amounts in theses bloods were measured by the end point method employing glycerol oxidase method. The neutral lipid reducing activity in each blood was expressed by a reducing rate relative to the value before the drug-administration.

The compounds of the present invention exhibited higher hypoglycemic activities and higher neutral lipid reducing activities as compared with CS-045 used as controls.

Compound No.	Dose (mg/kg)	% decrease of glucose	% decrease of TC	% decrease of TG
I-2b-6	30	10.5	19.5	13.8
CS-045	300	17.7	7.1	36.9



CS-045

TEST EXAMPLE 3: Measurement of aldose-reductase inhibitory activities

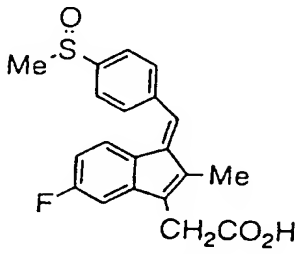
Rat kidney AR was prepared as follows; Rat kidney was

perfused by ice-cold saline to remove blood and then homogenized in a Teflon homogenizer with 3 time volumes of cold 5 mM Tris-HCℓ buffer (pH 7.4). The homogenate was centrifuged at 45,000 x g for 40 minutes to remove insoluble materials, and the supernatant fraction was dialyzed overnight against 0.05 M sodium chloride solution. The dialyzed solution was centrifuged again at 11,000 × g for 20 minutes and the supernatant fraction was used as an aldose reductase sample.

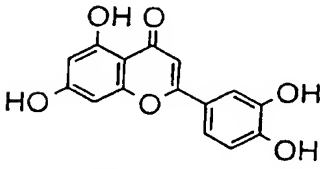
Determination of AR and effects of test compounds

AR activity was assayed by the modified method of Inukai et al. (Jpn. J. Pharmacol. 61, 221-227, 1993). The absorbance of NADPH (340 nm), oxidation of the co-factor for AR, was determined by spectrophotometer (UV-240, Shimadzu, Kyoto). The assay was carried out in 0.1M sodium phosphate (pH 6.2) containing 0.4M lithium sulfate, 0.15 mM NADPH, the enzyme, various concentrations of test compounds and 10 mM DL-glyceraldehyde. The reference blank contained all of the above ingredients, except for DL-glyceraldehyde. The reaction was started by addition of the substrate (DL-glyceraldehyde). The reaction rate was measured at 30°C for 2 minutes. All test compounds were dissolved in dimethyl sulfoxide (DMSO). The final concentration of DMSO in reaction mixture never exceeded 1%.

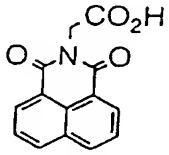
Compound No.	Concentration(μ M)	% inhibition
I-1a-4	30	100.0
I-1b-14	30	53.4
I-2b-6	100	36.3
I-2b-10	30	23.3
I-3b-5	30	49.6
CS-045	100	0
Sulindac	30	54.0
Quercetin	30	10.8
Alrestatin	100	0



Sulindac



Quercetin



Alrestatin

The compounds of the present invention exhibited equivalent or stronger aldose-reductase inhibitory activities than sulindac, quercetin or alrestatin used as control. Further, CS-045 exhibited no activities.

FORMULATION EXAMPLE 1

Tablets

The compound of the present invention	1.0 g
Lactose	5.0 g
Crystal cellulose powder	8.0 g
Corn starch	3.0 g
Hydroxypropyl cellulose	1.0 g
CMC-Ca	1.5 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were mixed by a usual method and then tabletted to produce 100 tablets each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 2

Capsules

The compound of the present invention	1.0 g
Lactose	3.5 g
Crystal cellulose powder	10.0 g
Magnesium stearate	0.5 g
Total	15.0 g

The above components were mixed by a usual method and then packed in No. 4 gelatin capsules to obtain 100 capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 3

Soft capsules

The compound of the present invention	1.00 g
PEG (polyethylene glycol) 400	3.89 g
Saturated fatty acid triglyceride	15.00 g
Peppermint oil	0.01 g
Polysorbate 80	0.10 g
Total	20.00 g

The above compounds were mixed and packed in No. 3 soft gelatin capsules by a usual method to obtain 100 soft capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 4

Ointment

The compound of the present invention	1.0 g (10.0 g)
Liquid paraffin	10.0 g (10.0 g)
Cetanol	20.0 g (20.0 g)
White vaseline	68.4 g (59.4 g)
Ethylparaben	0.1 g (0.1 g)
l-menthol	0.5 g (0.5 g)
Total	100.0 g

The above components were mixed by a usual method to obtain a 1% (10%) ointment.

FORMULATION EXAMPLE 5

Suppository

The compound of the present invention	1.0 g
Witepsol H15*	46.9 g
Witepsol W35*	52.0 g
Polysorbate 80	0.1 g
Total	100.0 g

*: Trademark for triglyceride compound

The above components were melt-mixed by a usual method and poured into suppository containers, followed by cooling for solidification to obtain 100 suppositories of 1 g each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 6

Granules

The compound of the present invention	1.0 g
Lactose	6.0 g
Crystal cellulose powder	6.5 g
Corn starch	5.0 g
Hydroxypropyl cellulose	1.0 g
Magnesium stearate	0.5 g
Total	20.0 g

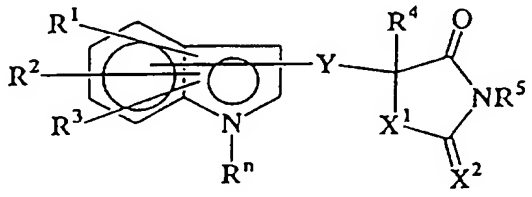
The above components were granulated by a usual method and packaged to obtain 100 packages each containing 200 mg of the granules so that each package contains 10 mg of the active ingredient.

INDUSTRIAL APPLICABILITY

Since the compound of the present invention has a hypoglycemic effect and an aldose-reductase inhibitory activity and has less toxicity, it is useful for preventing or treating diabetic complications including diabetic eye diseases (such as diabetic cataract and diabetic retinopathy), diabetic neuropathy, diabetic nephropathy, diabetic gangrene, and the like.

CLAIMS

1. An indole type thiazolidine compound of the following formula (I) and its salt:



(I)

wherein X^1 is S or O;

X^2 is S, O or NH;

Y is CR^6R^7 (R^6 is a hydrogen atom, a C_1-C_7 alkyl group or a C_3-C_7 cycloalkyl group, and R^7 is a hydrogen atom, a C_1-C_7 alkyl group or a C_3-C_7 cycloalkyl group, or forms a bond together with R^4);

R^1 is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring and is a C_1-C_{10} alkyl group, a C_2-C_{10} alkenyl group, a C_2-C_{10} alkynyl group, a C_1-C_{10} alkoxy group, a C_2-C_{10} alkenyloxy group, a C_1-C_{10} alkylthio group, a C_1-C_{10} monoalkylamino group or a di-C_1-C_{10} alkylamino group (each of said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyloxy, C_1-C_{10} alkylthio, C_1-C_{10} monoalkylamino and di-C_1-C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1-C_7 alkyl group), or

$-W_k-V_\ell-Z$ (Z is a C_3-C_{10} cycloalkyl group, a C_3-C_7 cycloalkenyl group, a C_6-C_{14} aromatic group, a C_1-C_{12} heterocyclic aromatic group (said heterocyclic aromatic

group may contain at most 5 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring), or a C_1-C_6 heterocycloaliphatic group (said heterocycloaliphatic group may contain at most 3 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring) (each of said C_3-C_{10} cycloalkyl, C_3-C_7 cycloalkenyl, C_6-C_{14} aromatic, C_1-C_{12} heterocyclic aromatic and C_1-C_6 heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7

cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group),

W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and

each of k and ℓ is 0 or 1),

-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different), or

R^1 may be a hydrogen atom when Y is bonded to the 4-, 5-, 6- or 7-position of an indole ring;

each of R^2 and R^3 is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring, and is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group (said C_1-C_7 alkyl and C_3-C_7 cycloalkyl groups may be substituted with a hydroxyl group), a C_1-C_7 alkoxy group, a benzyloxy group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group, a pyrimidinyl group, a pyridazinyl group, a furanyl group, a thienyl group, a pyrrolyl group, a pyrazolyl group, an imidazolyl group, a pyranyl group, a quinolyl group, a

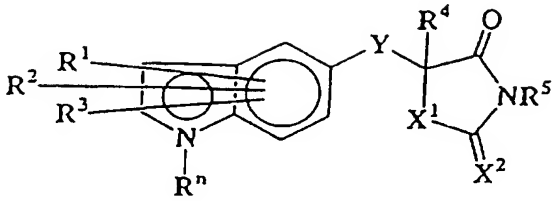
benzoxazolyl group, a benzothiazolyl group or a benzimidazolyl group (each of said phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl and benzimidazolyl groups may be substituted with at most 5 members selected from the group consisting of a hydroxyl group, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group and a halogen atom), a hydroxyl group or a halogen atom;

R^4 is a hydrogen atom or a C_1-C_7 alkyl group, or forms a bond together with R^7;

R^5 is a hydrogen atom or a carboxymethyl group; and

R^n is a substituent at the 1-position of an indole ring, and is a hydrogen atom, C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_4 alkoxymethyl group, an aryloxymethyl group, a C_1-C_4 alkylaminomethyl group, a substituted acetamidemethyl group, a substituted thiomethyl group, a carboxyl group, a C_1-C_7 acyl group, an arylcarbonyl group, a C_1-C_4 alkoxycarbonyl group, an aryloxycarbonyl group, a C_1-C_4 alkylaminocarbonyl group, an arylaminocarbonyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkoxyalkyloxy group, a trialkylsilyl group, a trialkylarylsilyl group, an alkylsulfonyl group or an arylsulfonyl group.

2. The indole type thiazolidine compound and its salt according to Claim 1, wherein the compound of the formula (I) is represented by the following formula (Ia):



(Ia)

wherein R^1 is a substituent at the 2-, 3-, 4-, 6- or 7-position of an indole ring and is a hydrogen atom, a C_1-C_{10} alkyl group, a C_2-C_{10} alkenyl group, a C_2-C_{10} alkynyl group, a C_1-C_{10} alkoxy group, a C_2-C_{10} alkenyloxy group, a C_1-C_{10} alkylthio group, a C_1-C_{10} monoalkylamino group or a di-C_1-C_{10} alkylamino group (each of said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyloxy, C_1-C_{10} alkylthio, C_1-C_{10} monoalkylamino and di-C_1-C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1-C_7 alkyl group), or

$-W_k-V_\ell-Z$ (among groups of Z as defined for the formula (I), said C_3-C_{10} cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl, said C_3-C_7 cycloalkenyl group is cyclohexenyl, cyclopentadienyl, 2-bicylo[2.2.1]heptenyl or 2,5-bicyclo[2.2.1]heptadienyl, said C_6-C_{14} aromatic group is phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C_1-C_{12} heterocyclic aromatic group is furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl,

oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl, pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl, pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl, benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl, benzothiazolyl, benzopyrazolyl, benzimidazolyl, benzotriazolyl, benzopyranyl, indolizinyl, purinyl, phthalazinyl, oxophthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxolyl, benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl, benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, or thianthrenyl, and said C_1-C_6 heterocycloaliphatic group is piperidyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, or tetrahydrofuranyl, (each of said C_3-C_{10} cycloalkyl, C_3-C_7 cycloalkenyl, C_6-C_{14} aromatic, C_1-C_{12} heterocyclic aromatic and C_1-C_6 heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a

trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group),

W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and

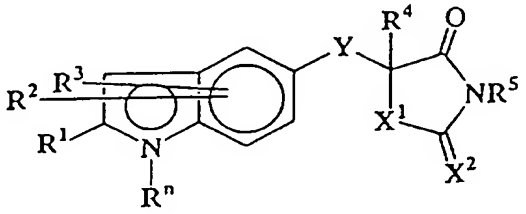
each of k and ℓ is 0 or 1),

-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different).

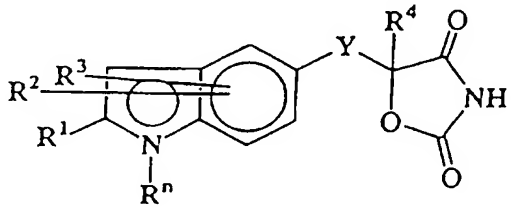
3. The indole type thiazolidine compound and its salt

according to Claim 2, wherein the compound of the formula (Ia) is represented by the formula (Ib):



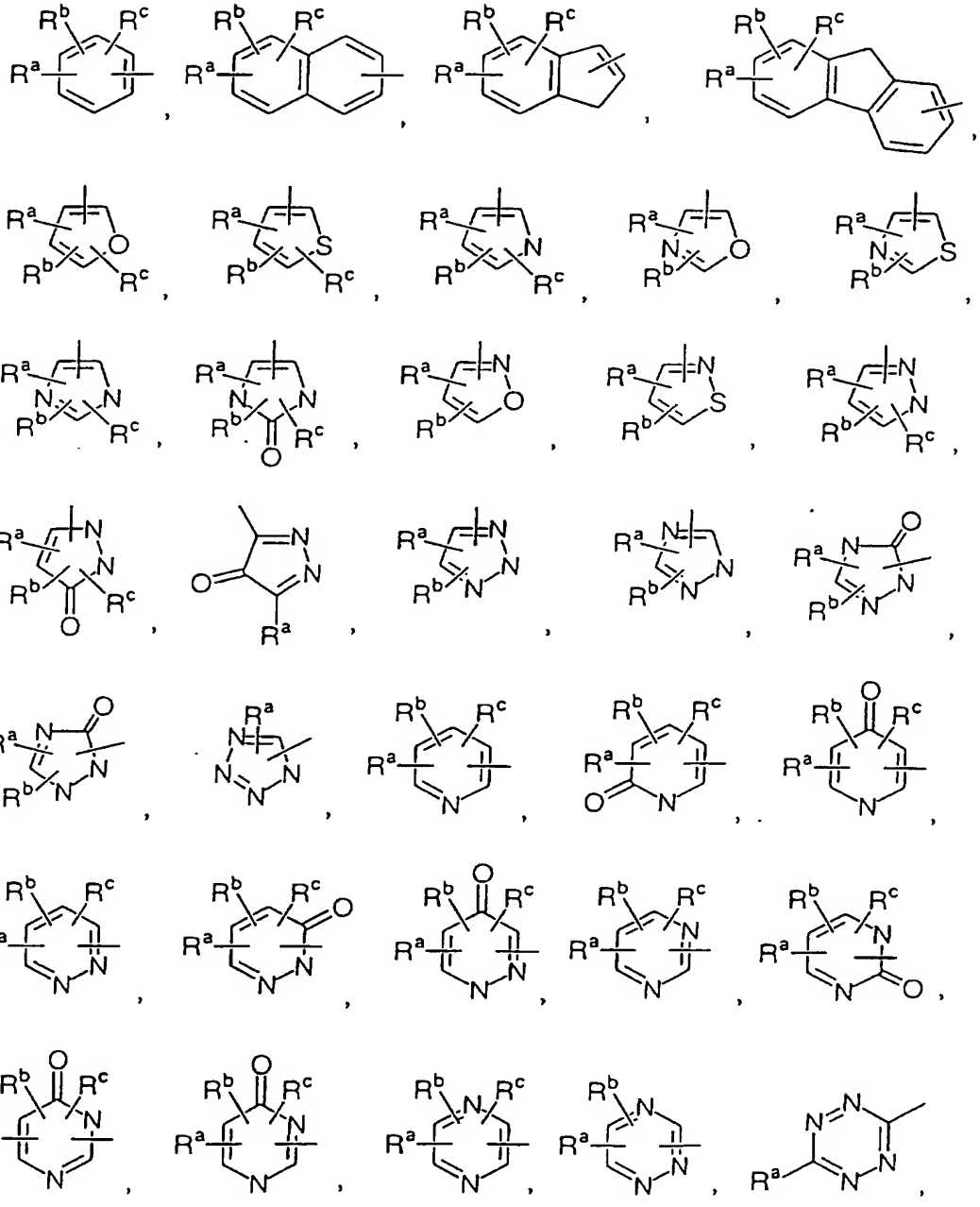
(Ib)

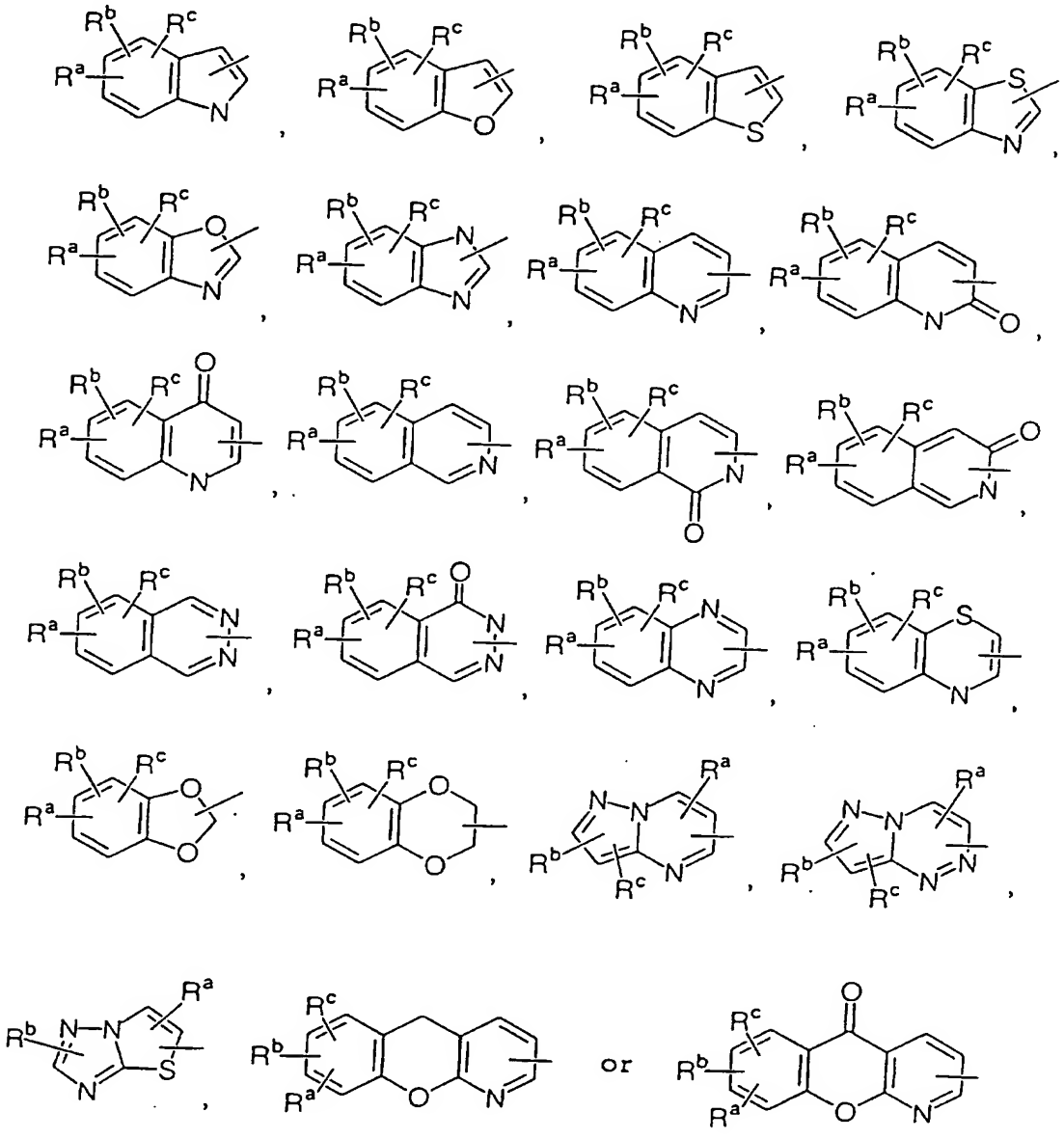
4. The indole type thiazolidine compound and its salt according to Claim 3, wherein the compound of the formula (Ib) is represented by the formula (Ic):



(Ic)

wherein R^1 is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, when two W's are present, such W's may be the same or different, and Z is





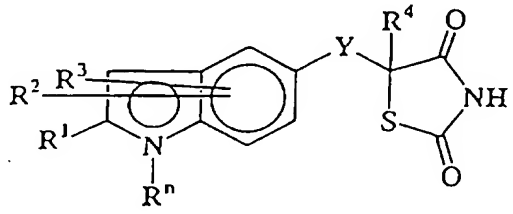
wherein each of R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a

C_3-C_6 cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and

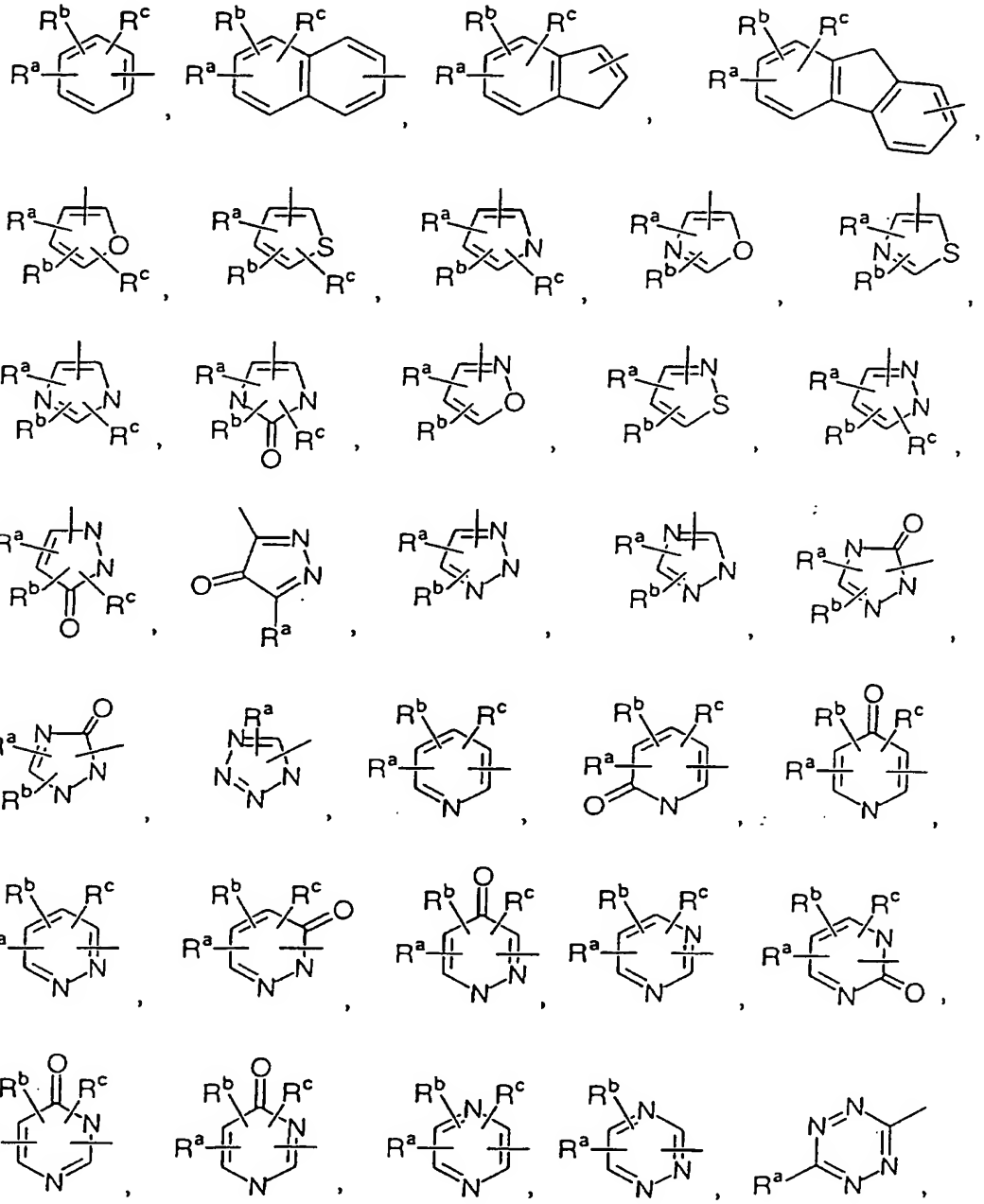
R^5 is a hydrogen atom.

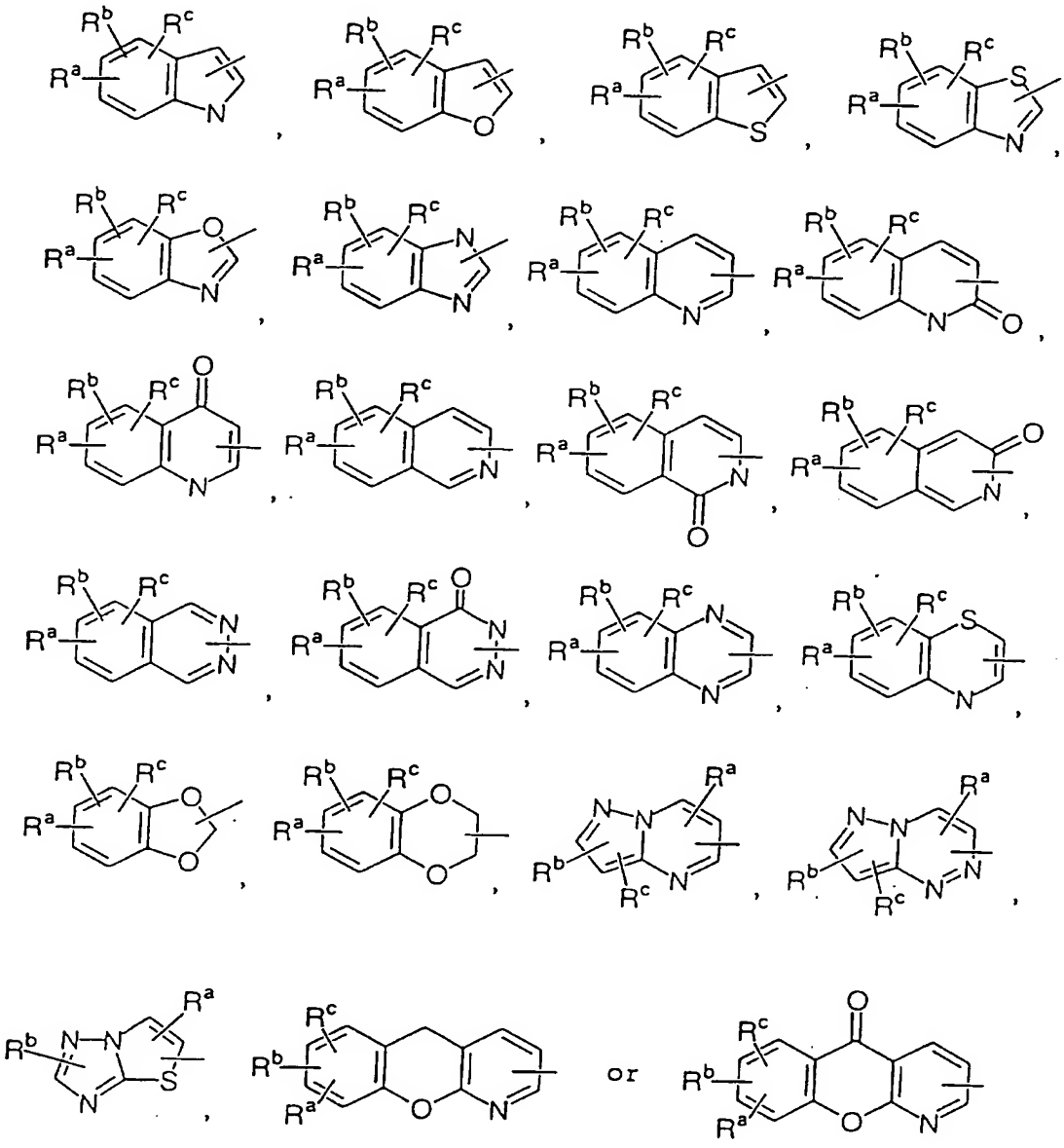
5. The indole type thiazolidine compound and its salt according to Claim 3, wherein the compound of the formula (Ib) is represented by the formula (Id):



(Id)

wherein R^1 is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, when two W's are present, such W's may be the same or different, and Z is





wherein each of R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

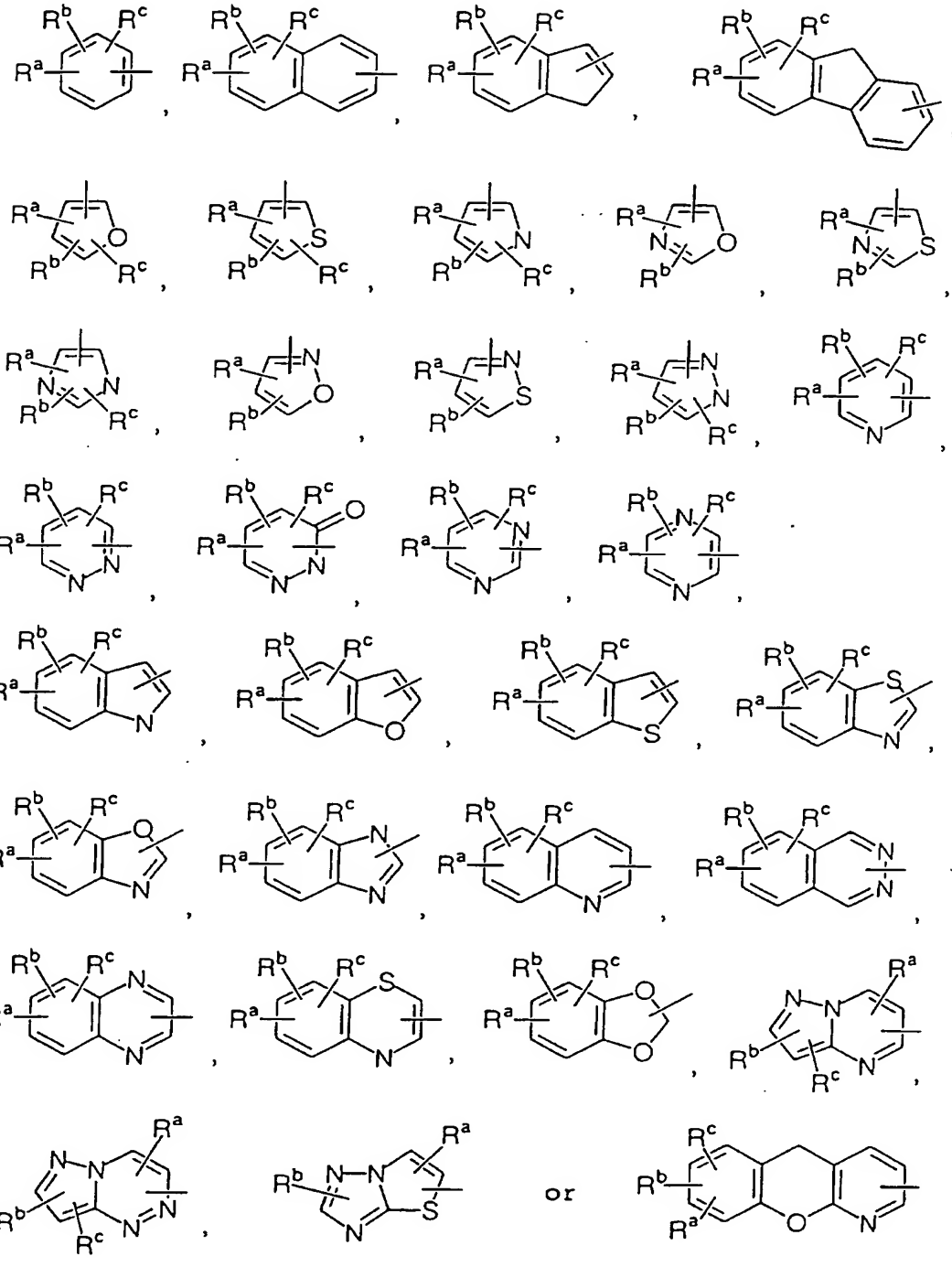
R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a

C_3-C_6 cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and

R^5 is a hydrogen atom.

6. The indole type thiazolidine compound and its salt according to Claim 5, wherein Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4);

R^1 is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups (provided that the first carbon atom bonded to N is not substituted with a hydroxyl group and the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group), when two W's are present, such W's may be the same or different, and Z is



wherein each R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^4 is a hydrogen atom or a methyl group, or forms a bond together with R^7; and

R^n is a substituent at the 1-position of an indole

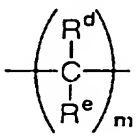
ring, and is a hydrogen atom, a C_1-C_3 alkyl group, a cyclopropyl group, a C_1-C_2 alkoxymethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C_1-C_3 alkoxy group and a trialkylsilyl group.

7. The indole type thiazolidine compound and its salt according to Claim 6, wherein:

R^1 is -W-Z, wherein W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 2 of hydroxyl, oxo and C_1-C_7 alkyl groups.

8. The indole type thiazolidine compound and its salt according to Claim 7, wherein:

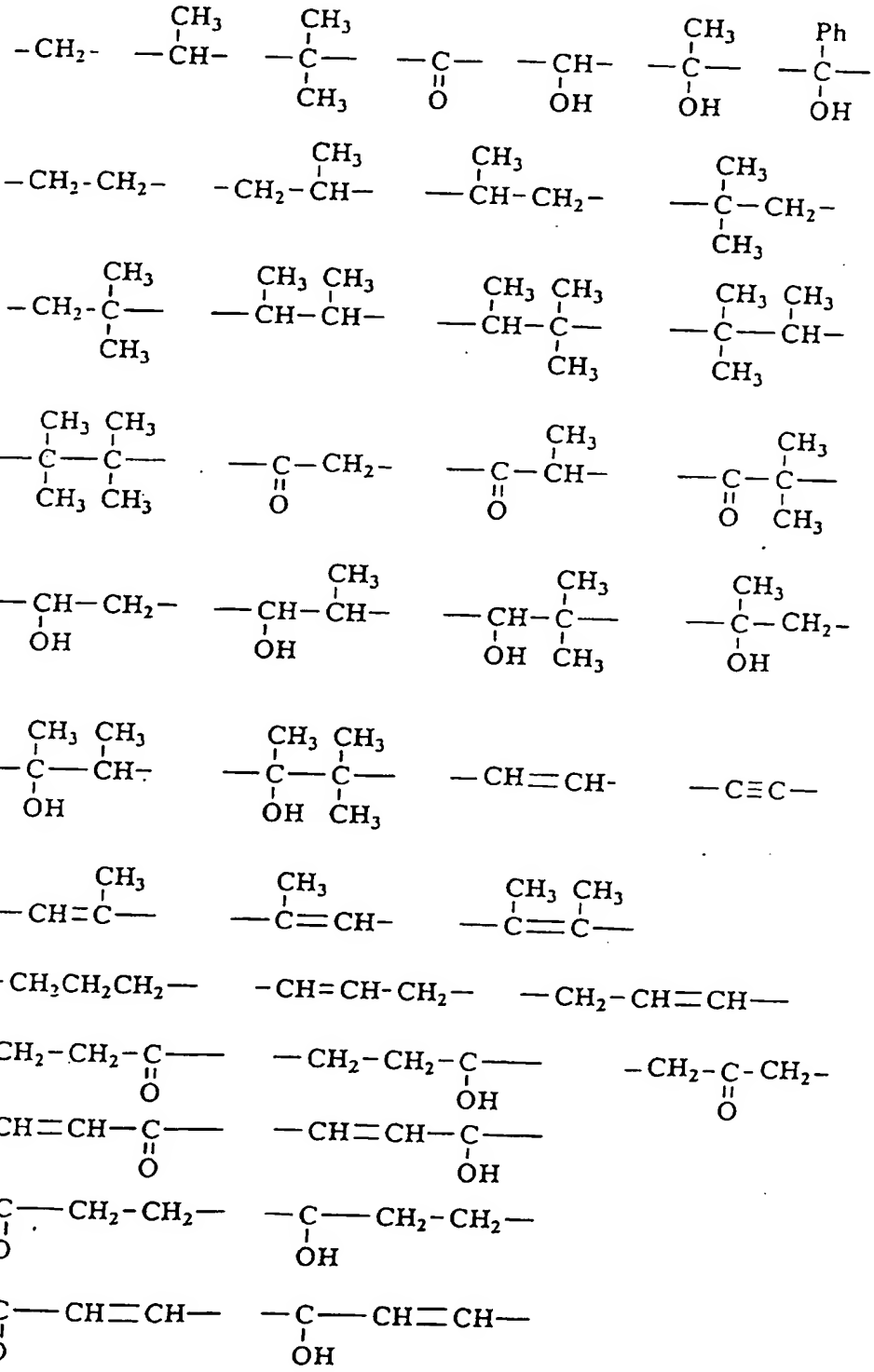
R^1 is -W-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond.

9. The indole type thiazolidine compound and its salt according to Claim 8, wherein:

R^1 is -W-Z, wherein W is

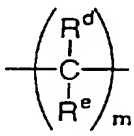


10. The indole type thiazolidine compound and its salt according to Claim 6, wherein:

R^1 is -V-Z, wherein V is S, SO or SO_2.

11. The indole type thiazolidine compound and its salt according to Claim 6, wherein:

R^1 is -W-V-Z, wherein W is



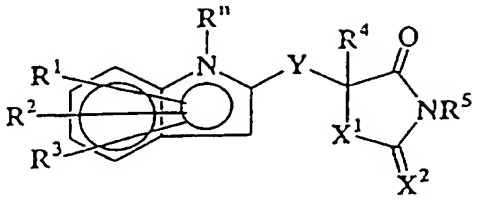
wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to N are not hydroxyl groups and also provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group),

V is NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group).

12. The indole type thiazolidine compound and its salt according to Claim 11, wherein:

R^1 is -W-V-Z, wherein -W-V- is $-CO-NR^8-$ (R^8 is a hydrogen atom or a C_1-C_3 alkyl group).

13. The indole type thiazolidine compound and its salt according to Claim 1, wherein the compound of the formula (I) is represented by the following formula (Ie):



(Ie)

wherein R^1 is a substituent at the 3-, 4-, 5-, 6- or 7-position of an indole ring, and is a C_1-C_{10} alkyl group, a C_2-C_{10} alkenyl group, a C_2-C_{10} alkynyl group, a C_1-C_{10} alkoxy group, a C_2-C_{10} alkenyloxy group, a C_1-C_{10} alkylthio group, a C_1-C_{10} monoalkylamino group or a di-C_1-C_{10} alkylamino group (each of said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyloxy, C_1-C_{10} alkylthio, C_1-C_{10} monoalkylamino and di-C_1-C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1-C_7 alkyl group), or

$-W_k-V_\ell-Z$ (among groups of Z as defined for the formula (I), said C_3-C_{10} cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl, said C_3-C_7 cycloalkenyl group is cyclohexenyl, cyclopentadienyl, 2-bicylo[2.2.1]heptenyl or 2,5-bicyclo[2.2.1]heptadienyl, said C_6-C_{14} aromatic group is phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C_1-C_{12} heterocyclic aromatic group is furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl, oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl,

pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl, pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl, benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl, benzothiazolyl, benzopyrazolyl, benzimidazolyl, benzotriazolyl, benzopyranyl, indolizinyl, purinyl, phthalazinyl, oxophthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxolyl, benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl, benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, or thianthrenyl, and said C_1-C_6 heterocycloaliphatic group is piperidyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, or tetrahydrofuranyl, (each of said C_3-C_{10} cycloalkyl, C_3-C_7 cycloalkenyl, C_6-C_{14} aromatic, C_1-C_{12} heterocyclic aromatic and C_1-C_6 heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a

methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group),

W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and

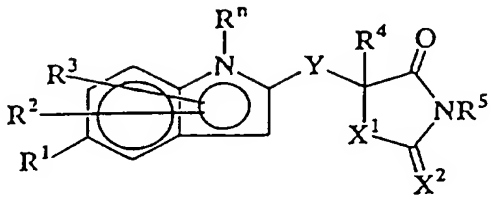
each of k and ℓ is 0 or 1),

-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different).

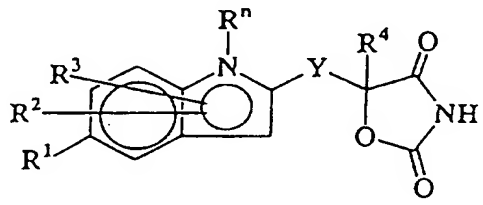
14. The indole type thiazolidine compound and its salt according to Claim 13, wherein the compound of the

formula (Ie) is represented by the formula (If):



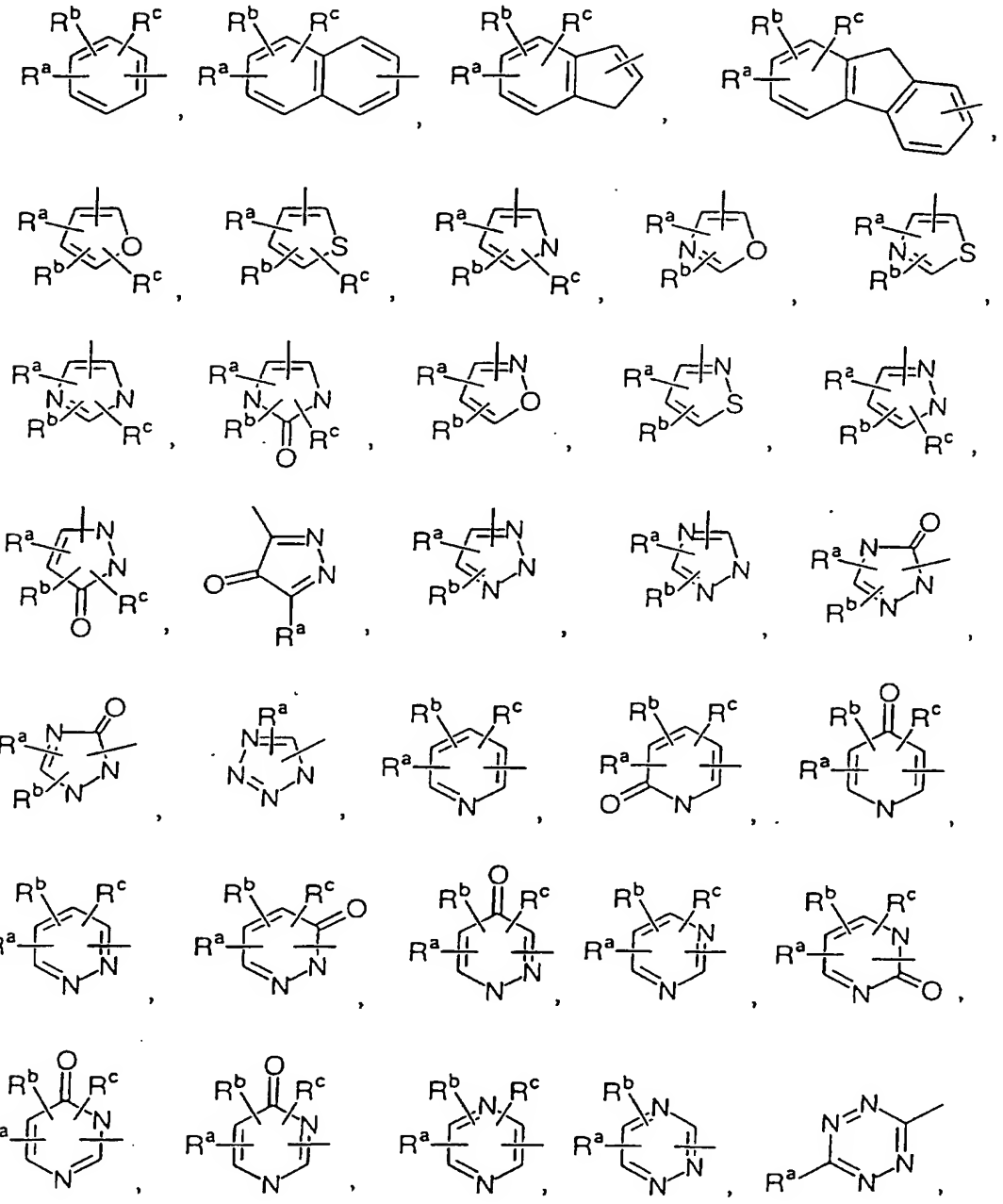
(If)

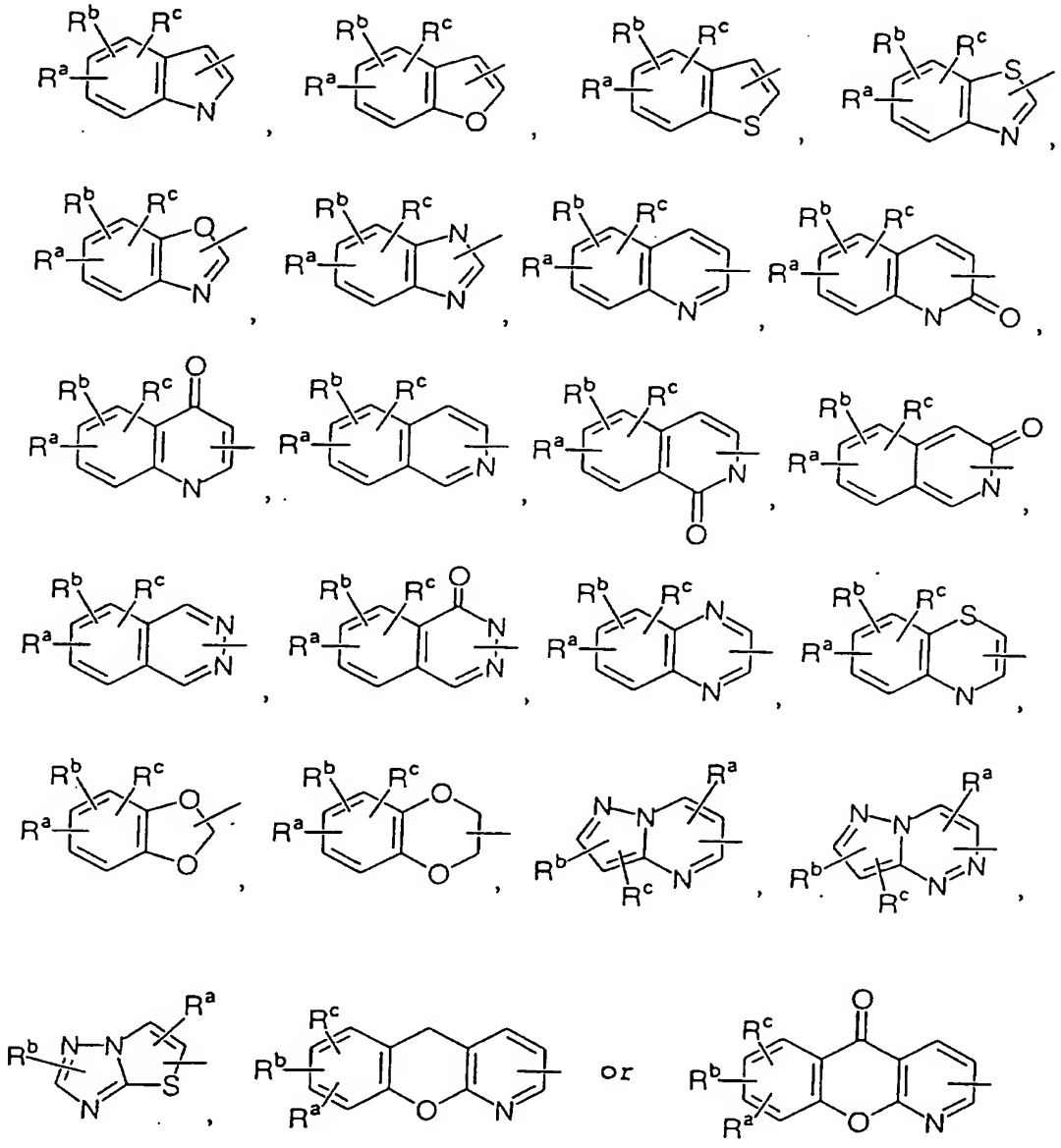
15. The indole type thiazolidine compound and its salt according to Claim 14, wherein the compound of the formula (If) is represented by the formula (Ig):



(Ig)

wherein R^1 is a substituent at the 5-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, when two W's are present, such W's may be the same or different, and Z is





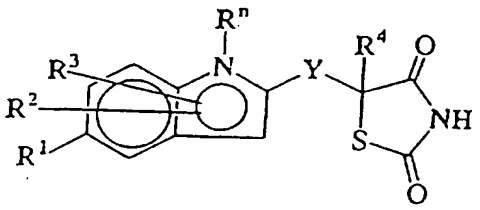
wherein each of R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a

C_3-C_6 cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and

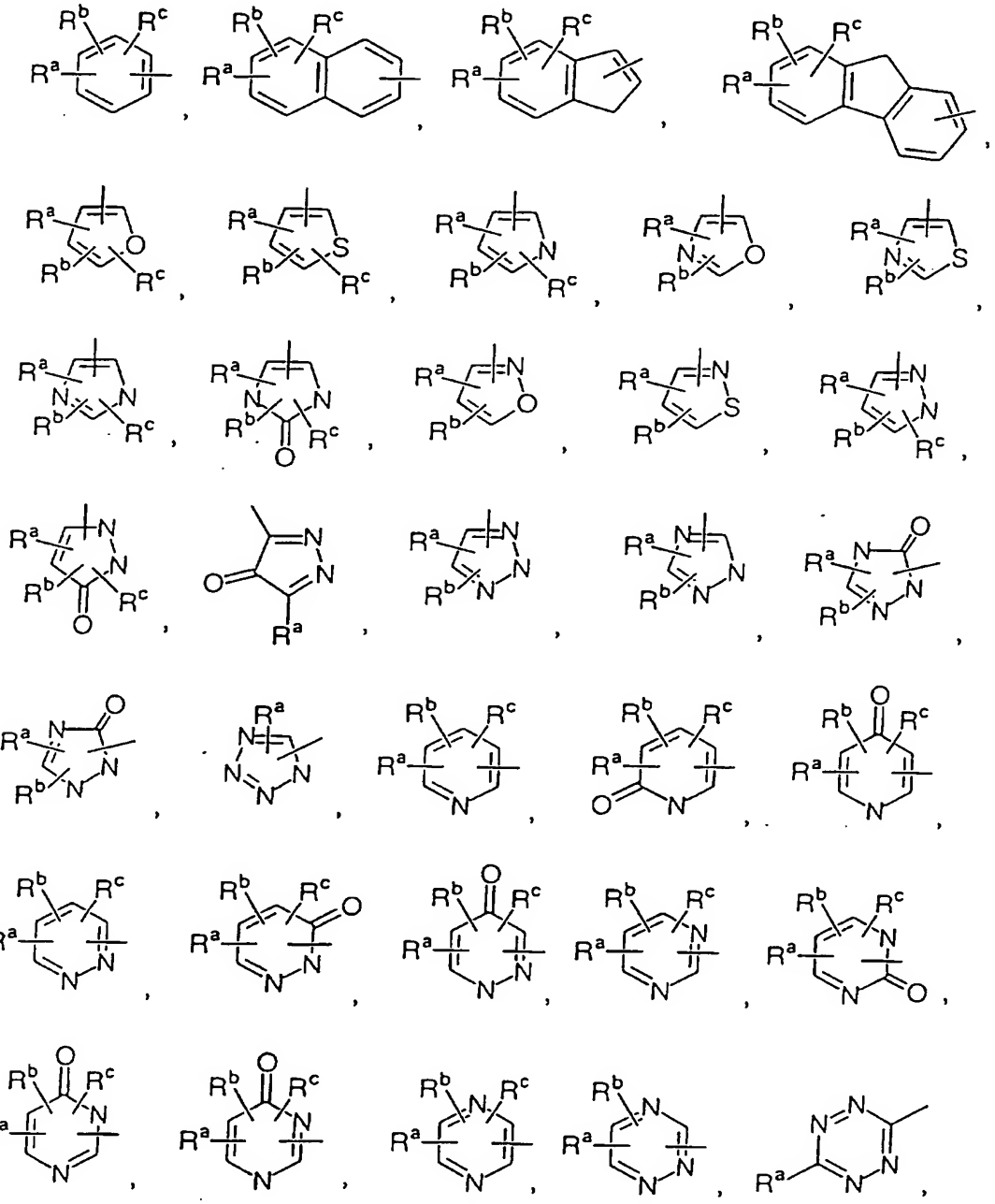
R^5 is a hydrogen atom.

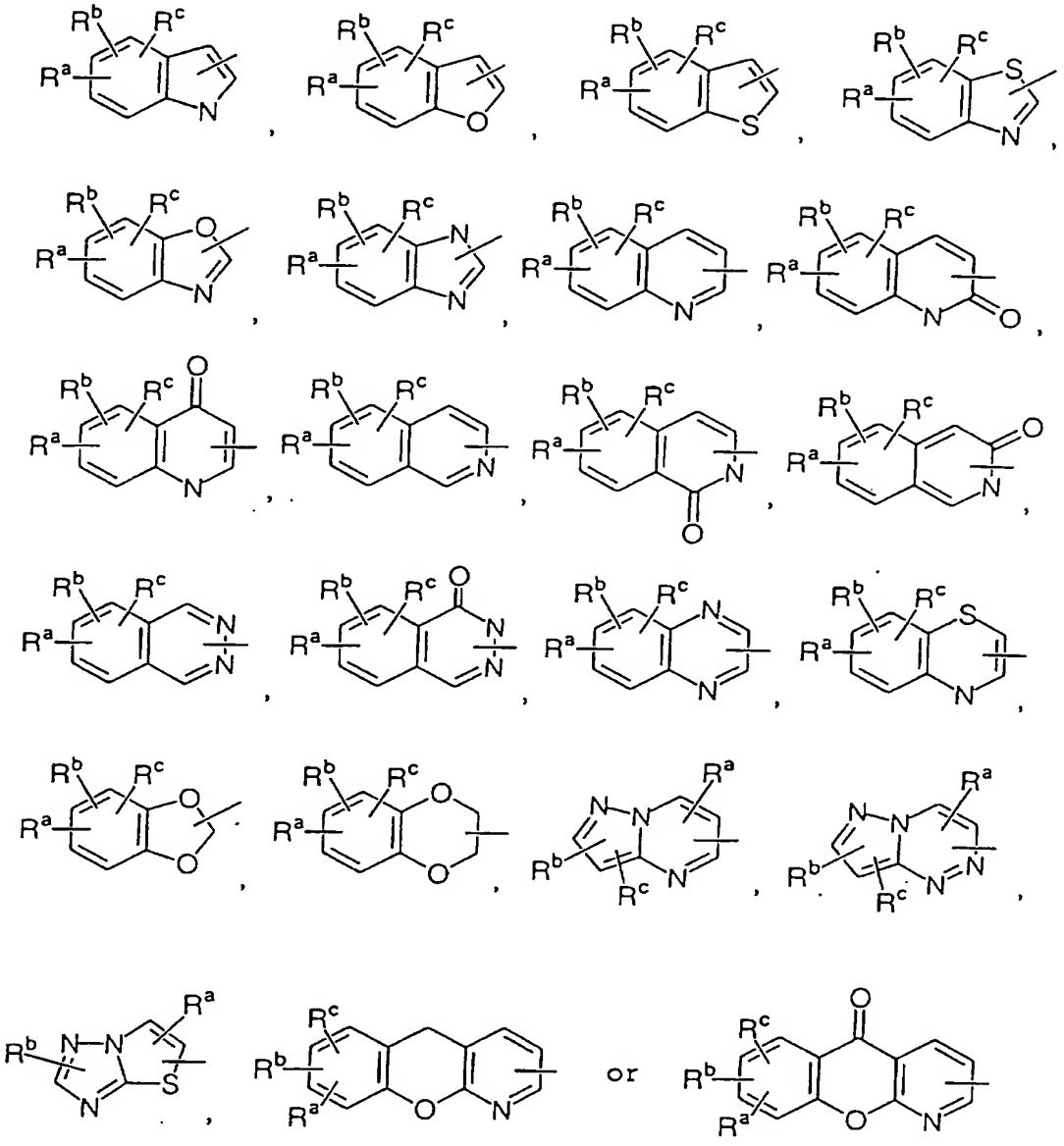
16. The indole type thiazolidine compound and its salt according to Claim 14, wherein the compound of the formula (If) is represented by the formula (Ih):



(Ih)

wherein R^1 is a substituent at the 5-posotion of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, when two W's are present, such W's may be the same or different, and Z is





wherein each of R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

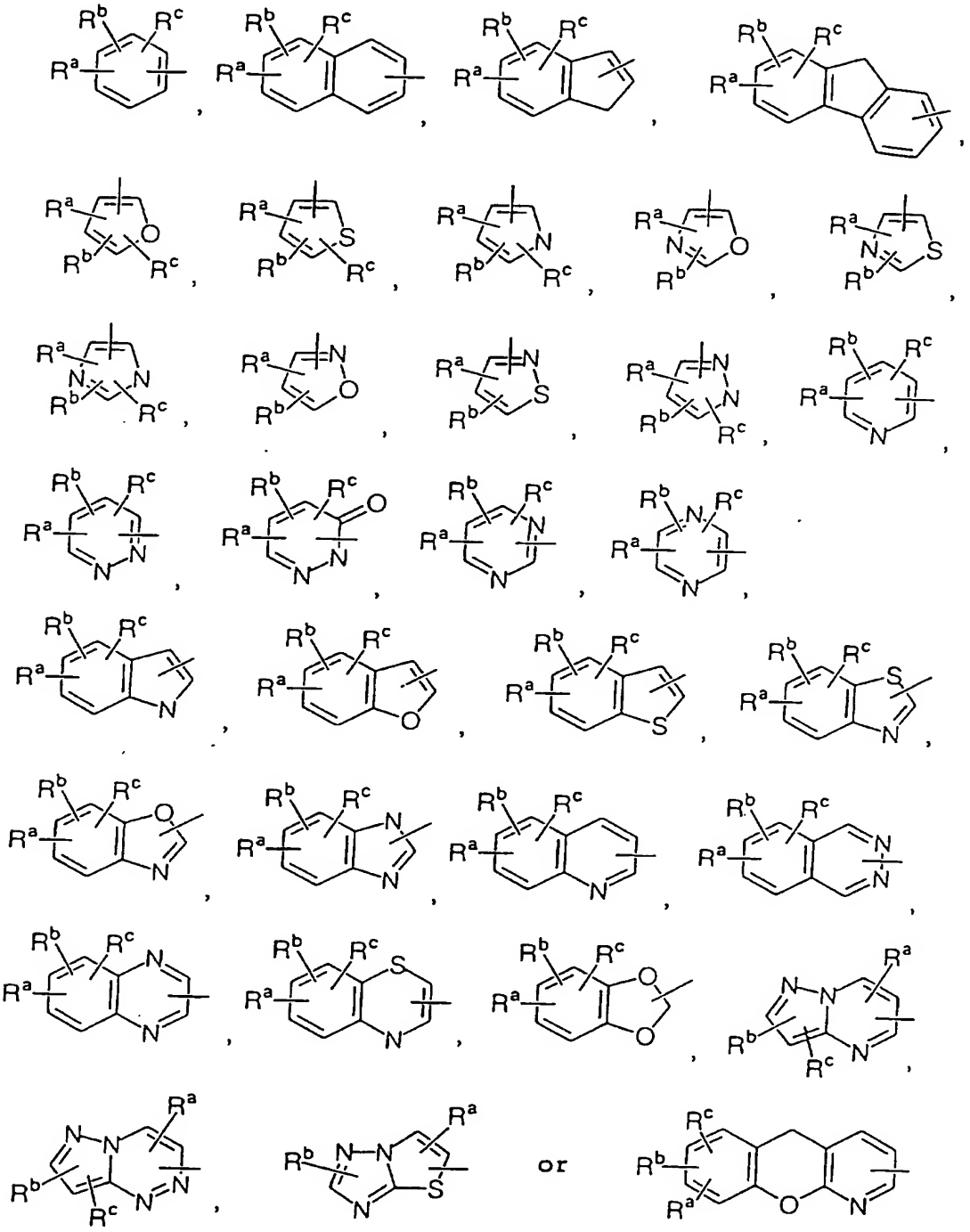
R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a

C_3-C_6 cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and

R^5 is a hydrogen atom.

17. The indole type thiazolidine compound and its salt according to Claim 16, wherein Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4);

R^1 is a substituent at the 5-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups (provided that the first carbon atom bonded to N is not substituted with a hydroxyl group and the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group), when two W's are present, such W's may be the same or different, and Z is



wherein each R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri-C_1-C_7-alkylsilyl group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^4 is a hydrogen atom or a methyl group, or forms a bond together with R^7; and

R^n is a substituent at the 1-position of an indole

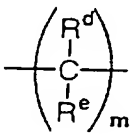
ring, and is a hydrogen atom, a C_1-C_3 alkyl group, a cyclopropyl group, a C_1-C_2 alkoxymethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C_1-C_3 alkoxy group and a trialkylsilyl group.

18. The indole type thiazolidine compound and its salt according to Claim 17, wherein:

R^1 is -W-Z, wherein W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 2 of hydroxyl, oxo and C_1-C_7 alkyl groups.

19. The indole type thiazolidine compound and its salt according to Claim 18, wherein:

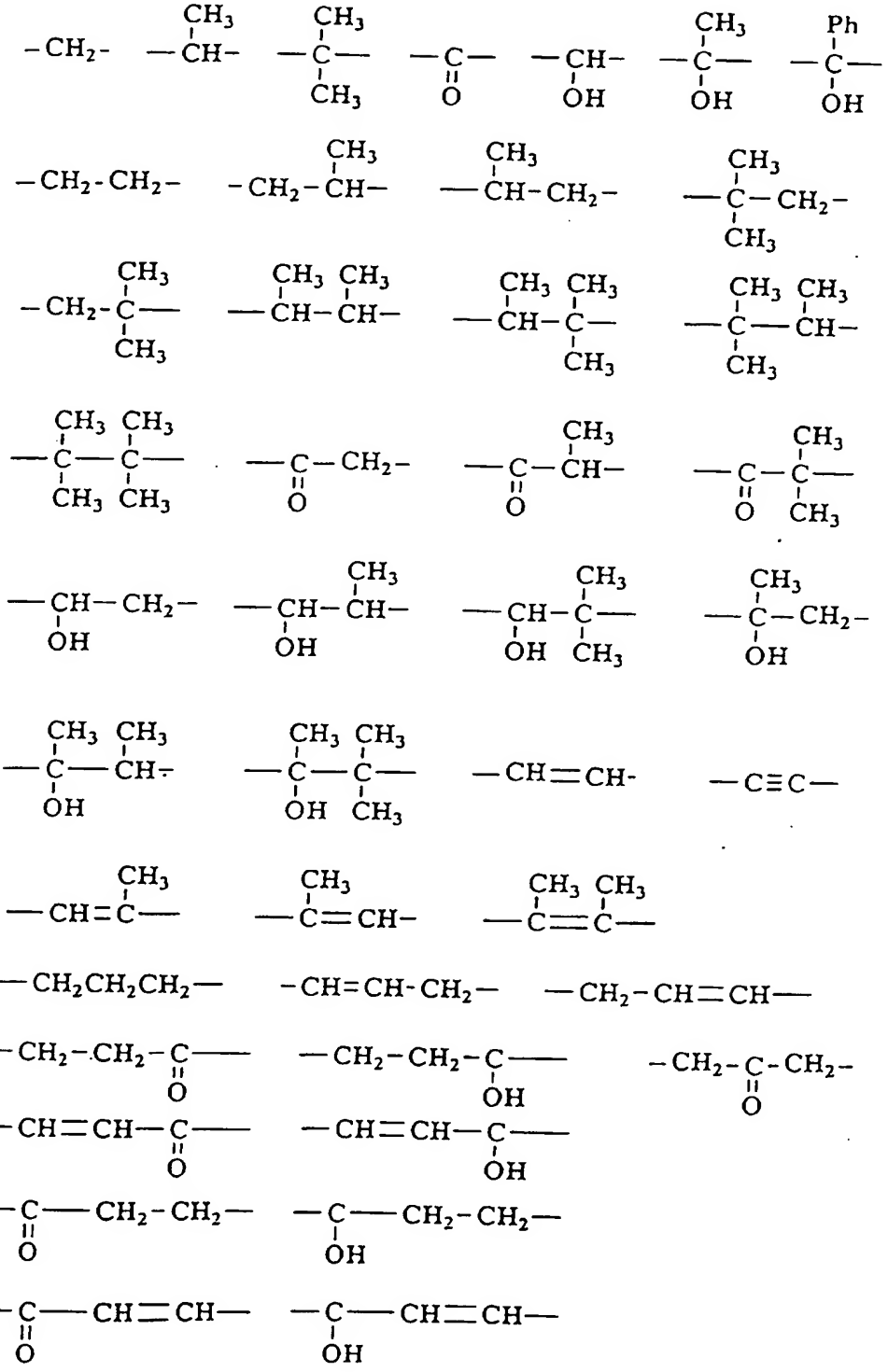
R^1 is -W-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond.

20. The indole type thiazolidine compound and its salt according to Claim 19, wherein:

R^1 is -W-Z, wherein W is

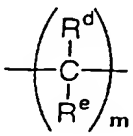


21. The indole type thiazolidine compound and its salt according to Claim 17, wherein:

R^1 is -V-Z, wherein V is S, SO or SO_2.

22. The indole type thiazolidine compound and its salt according to Claim 17, wherein:

R^1 is -W-V-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to N are not hydroxyl groups and also provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group), and

V is NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group).

23. The indole type thiazolidine compound and its salt according to Claim 22, wherein:

R^1 is -W-V-Z, wherein -W-V- is $-CO-NR^8-$ (R^8 is a hydrogen atom or a C_1-C_3 alkyl group).

24. The indole type thiazolidine compound and its salt according to Claim 9, 10, 12, 20, 21 or 22, wherein:

Y is $-CH_2-$; and

R^4 is a hydrogen atom.

25. The indole type thiazolidine compound and its salt according to Claim 9, 10, 12, 20, 21 or 22, wherein:

Y is CHR^7 (R^7 forms a bond together with R^4); and

R^4 forms a bond together with R^7.

26. A hypoglycemic agent containing the indole type thiazolidine compound or its salt according to Claim 1 as an active agent.

27. An aldose reductase inhibitor containing the indole type thiazolidine compound or its salt according to Claim 1 as an active agent.

28. A pharmaceutical agent for preventing and treating diabetes mellitus and diabetic complications, which contains the indole type thiazolidine compound or its salt according to Claim 1 as an active agent.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/JP 96/00403

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D417/06 C07D413/06 C07D417/14 A61K31/425 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 587 377 (LILLY CO ELI) 16 March 1994 cited in the application see claims	1-28
X	GB,A,2 080 803 (PFIZER) 10 February 1982 cited in the application see claims	1-28
X	EP,A,0 047 109 (ONO PHARMACEUTICAL CO) 10 March 1982 cited in the application see claims	1-28
X	EP,A,0 343 643 (WARNER LAMBERT CO) 29 November 1989 cited in the application see claims	1-25

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 1996	23.05.1996

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Henry, J

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 96/00403

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 143 927 (BOSCHELLI DIANE H ET AL) 1 September 1992 see the whole document ---	1-25
X	US,A,3 320 282 (MANFRED SCHACH VON WITTENAU ET AL) 16 May 1967 ---	1-25
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 21, no. 1, January 1978, WASHINGTON US, pages 82-87, XP002002903 MICHAEL R. HARNDEN ET AL: "Thiazolinone analogues of indolmycin with antiviral and antibacterial activity" cited in the application see the whole document ---	1-25
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 10, no. 9, September 1967, WASHINGTON US, pages 852-855, XP002002904 EDWARD J. GLAMKOWSKI ET AL: "A new class of potent decarboxylase inhibitors.Beta-(3-indolyl)-alpha-hydrazinopropionic acids" cited in the application see the whole document ---	1-25
X	CHEMICAL ABSTRACTS, vol. 101, no. 26, 24 December 1984 Columbus, Ohio, US; abstract no. 239482z, GALAN ALFONSO ET AL: "Derivatives of rhodanine as spectrophotometric analytical reagents.Determination of copper" page 574; XP002002905 cited in the application see abstract & ANAL.LETT., vol. 17, 1984, pages 1447-1462, ---	1-25
X	CHEMICAL ABSTRACTS, vol. 94, no. 14, 6 April 1981 Columbus, Ohio, US; abstract no. 112466d, page 633; XP002002906 cited in the application see abstract & JP,A,80 096 941 (MITSUBISHI PAPER MILLS,LTD) 23 July 1980 -----	1-25

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Inter nal Application No
PCT/JP 96/00403

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INTERNATIONAL SEARCH REPORT

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Inter nal Application No
PCT/JP 96/00403

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		GB-A,B	2134105	08-08-84
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